CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 010104

Name: Mephyton® (Phytonadione) Tablets, 5 mg

Sponsor: Merck & Company, Inc.

Approval Date: September 30, 1955

Indication, per original approval:
Mephyton is recommended for non-emergent use in controlling anticoagulant-induced prothrombin deficiency as produced by coumarins and indanediones.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 010104

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Approvable Letter	
Labeling	**X**
Division Director's Memo	
Labeling Review(s)	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology / Toxicology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology & Biopharmaceutics Review(s)	
Other Review(s)	
Administrative and Correspondence Documents	**X**
Post-approval DESI Review and FR Notice	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 010104

APPROVAL LETTER

NDA 10104

AF 12-611

Merck & Company, Inc.
Attention: Mr. J. M. Young
Rahway, New Jersey

SEP 30 1955

Gentlemen:

This will acknowledge your new drug application dated August 1, 1955 submitted pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act for the preparation Vitamin K_1 Tablets, 5 mg.

Although this submission was presented as a supplement to your effective application for Emulsion of Vitamin K_1 (NDA 8448), it is being considered as a separate new drug application.

This application was filed on August 3, 1955.

We have completed our study of this application and in accordance with the provisions of the regulation under section 505(c) of the Federal Food, Drug, and Cosmetic Act it has become effective.

We are requesting information on the derivation of the factor (b) (4) used in the equation for calculating the vitamin K_1 content of the finished tablets.

Please submit five copies of the final printed label and labeling and three finished market packages of the drug when available.

Sincerely yours,

Ralph G. Smith, M.D.
Chief New Drug Branch
Division of Medicine

Enclosure
Effective Paragraphs

cc NY
cc Div Med
EQK
RGSmith:hdw 9/30/55

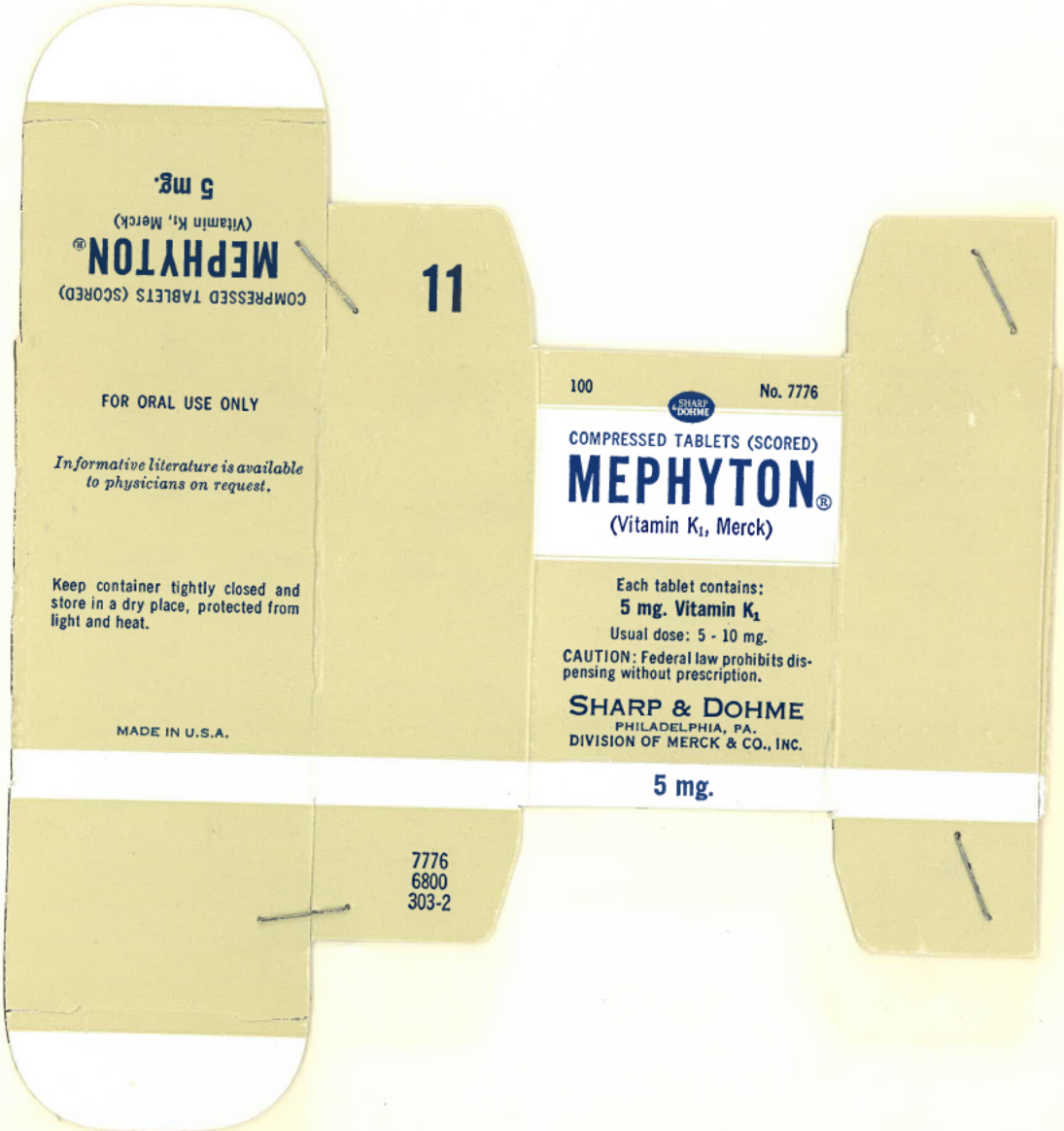
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 010104

LABELING


100 Tablets
No. 7776
Compressed Tablets (Scored)
MEPHYTON®
(VITAMIN K1, MERCK)
5 mg.
CAUTION: Federal law prohibits dispensing without prescription.
SHARP & DOHME
DIVISION OF MERCK & CO., INC.
Informative literature is available to physicians on request.
FOR ORAL USE ONLY
Usual dose: 5—10 mg.
Keep container tightly closed and store in a dry place, protected from light and heat.


5 mg.
(Vitamin K1, Merck)
MEPHYTON®
COMPRESSED TABLETS (SCORED)
FOR ORAL USE ONLY
Informative literature is available to physicians on request.
Keep container tightly closed and store in a dry place, protected from light and heat.
MADE IN U.S.A.
11
100
No. 7776
COMPRESSED TABLETS (SCORED)
MEPHYTON®
(Vitamin K1, Merck)
Each tablet contains:
5 mg. Vitamin K1
Usual dose: 5 - 10 mg.
CAUTION: Federal law prohibits dispensing without prescription.
SHARP & DOHME
PHILADELPHIA, PA.
DIVISION OF MERCK & CO., INC.
5 mg.
7776
6800
303-2

FOR PHYSICIANS' REQUEST

SHARP & DOHME

DIVISION OF MERCK & CO., INC.

TABLETS OF

MEPHYTON*®

(Brand of Vitamin K_1)

Vitamin K_1 (2-methyl-3-phytyl-1,4-naphthoquinone) is far superior in combating the anticoagulant effect of prothrombin-depressing agents than are menadione and other synthetic vitamin K-like substances. It also is valuable in the treat-

*MEPHYTON is the registered trademark of MERCK & CO., INC., for its brand of vitamin K_1.

ment of hypoprothrombinemia due to other causes. The oral preparation is indicated for non-emergent control of over-prolonged prothrombin times—when bleeding is neither present nor considered an early threat. (Emulsion of MEPHYTON for intravenous administration is available for use in actual or immediately threatened emergencies.)

USES

MEPHYTON is recommended for non-emergent use in controlling anticoagulant-induced prothrombin deficiency—as produced by coumarins (Dicumarol, Cumopyran, Tromexan, Coumadin Sodium [warfarin sodium], Marcoumar) and indanediones (Danilone, Indon, Dipaxin, Hedulin).

This use of MEPHYTON allows for smoother, safer continuous use of prothrombin-depressing anticoagulants, thus facilitating the task of the physician and increasing the therapeutic advantage to the patient.

The time for response to oral MEPHYTON depends on the anticoagulant being used, the degree of prothrombin deficiency, the dose of MEPHYTON, and the general condition of the patient. In general, after oral administration, beneficial effects are apparent in 6 to 10 hours. When quite small doses of MEPHYTON are chosen—as they should be for non-emergent prothrombin control—the response to a single dose may vary, necessitating repeated dosage in some cases. It is advantageous to use small oral doses of MEPHYTON because certain effects are avoided or minimized. These effects are (1) refractoriness to further anticoagulant therapy and (2) a drop in prothrombin below the therapeutically effective anticoagulant level.

The ideal goal of treatment with oral MEPHYTON is to maintain a prothrombin level which is both safe and effective in preventing undue blood coagulation. This requires a careful adjustment of dosage as discussed in subsequent sections.

MEPHYTON has been used at the end of anticoagulant therapy simply to speed the return of prothrombin to normal.

Also, for preoperative patients receiving anticoagulant therapy MEPHYTON—though preferably by the intravenous route—may be used preceding operation to restore a safer prothrombin level for the operative period, with postoperative resumption of the anticoagulant if necessary.

Other hypoprothrombinemias are amenable to treatment with tablets of MEPHYTON. The oral preparation is indicated, again in non-emergencies, when hypoprothrombinemia results from: inadequate absorption of vitamin K caused by intestinal deficiency of bile secondary to obstructive jaundice or biliary fistula (bile salts must also be given); inadequate absorption of vitamin K due to gastrointestinal disease as sprue, ulcerative colitis and celiac disease or to extensive surgical removal of gastrointestinal tissue (bile salts may be needed); inadequate endogenous production of vitamin K due to the inhibition of intestinal bacteria by oral sulfonamides or antibiotics; the toxic action of agents such as salicylates and phenylbutazone; neo-natal deficiency of prothrombin (for prophylaxis and only by administration to the mother at least 12 to 24 hours before delivery); dietary deficiency of vitamin K (extremely rare) and hepatic disease. In general the response of so caused hypoprothrombinemias to vitamin K_1 should be excellent, though in the more marked but still non-emergent hypoprothrombinemias intravenous administration may be wiser. However, in the case of hepatic disease response to vitamin K is often poor, being limited by the capacity of the liver to utilize the vitamin. (Based on the same principle the response of prothrombin level to vitamin K has been used as a measure of hepatic function.)

DOSAGE

As an antidote to anticoagulant effects the dosage of MEPHYTON for non-emergent prothrombin control is 5 to 10 mg. As little as 1 to 2.5 mg. have been used with encouraging results but this very low dosage is not generally recommended until more data on its use are available. If in 12 to 48 hours after medication with 5 to 10 mg. of MEPHYTON the prothrombin time has not been satisfactorily shortened the dose should be repeated. If the situation has been misjudged and the prothrombin time has continued to increase, intravenous administration of Emulsion of MEPHYTON may be necessary.

Small doses of oral MEPHYTON are strongly advised in order that the chance of undue interference with anticoagulant therapy may be minimized.

Fifteen to 25 mg. doses or even more of oral MEPHYTON may occasionally be selected if in the judgment of the physician the circumstances call for relatively vigorous action but do not require the intravenous use of Emulsion of MEPHYTON.

Up to 50 mg. of MEPHYTON, given at least 24 hours preoperatively (or 12 hours preoperatively if intravenously administered), along with temporary discontinuation of the anticoagulant, is recommended for restoration of prothrombin to a safer limit for the operative period

with its greatly augmented hazard of hemorrhage. For this 75% of the normal prothrombin level has been advised.

In general the response to therapy and the future course of action should be determined on the basis of the patient's clinical reaction and on repeated prothrombin time determinations.

Dosage for hypoprothrombinemia due to other causes also varies widely and depends on the nature and severity of the condition. *Whenever the endogenous supply of bile to the gastrointestinal tract is lessened, bile salts must be given along with orally administered MEPHYTON.* In obstructive jaundice or biliary fistula as little as 2 mg. daily may suffice, yet as much as 20 mg. or more a day may be required; in gastrointestinal disorders interfering with vitamin absorption usually 5, but up to 15 mg. or more daily, may be needed; as an antidote to toxicity from salicylates or other drugs 25 to 50 mg. or more is recommended; for hypoprothrombinemia induced by oral sulfonamides or antibiotics up to 15 mg.; in hepatic disease 50 mg. given intravenously three times a week has been reported useful—trial with orally administered MEPHYTON is justified; for hemorrhagic disease of the newborn 0.5 to 2 mg. is considered adequate for prophylaxis by administration to the mother.

As previously stated the intravenous (rather than the oral) preparation of MEPHYTON is specifically indicated for emergencies; it is also recommended in situations where oral medication is impractical or contraindicated.

CAUTIONS

When oral vitamin K_1 is used to correct undue anticoagulant-induced hypoprothrombinemia, while anticoagulant therapy is still indicated, it should be remembered that the patient already prone to abnormal clotting may occasionally be re-exposed to the same hazards of intravascular clotting that existed prior to initiation of anticoagulant therapy. MEPHYTON is not a clotting agent, but overzealous vitamin K_1 therapy resulting in restoration of the prothrombin time to or too near normal may thus also restore the pre-existent conditions which originally predisposed to thrombo-embolic phenomena. Therefore dosage of MEPHYTON should be kept as low as possible and prothrombin times should be checked regularly so that the prothrombin may be properly balanced between levels protecting the patient from abnormal clot formation on the one hand and pathologic hypoprothrombinemic bleeding on the other.

Temporary resistance to prothrombin-depressing anticoagulants may result, especially from the use of the larger doses of oral MEPHYTON. These larger doses of MEPHYTON should be avoided unless considered absolutely essential. If relatively large doses of vitamin K_1 have been used it may be necessary in re-instituting anticoagulant therapy to use somewhat larger doses of the prothrombin-depressing anticoagulant or to use an anticoagulant acting on a different principle, such as heparin sodium.

HOW SUPPLIED

Tablets of MEPHYTON are supplied as 5 mg. tablets, in bottles of 100.

SHARP & DOHME

SHARP & DOHME
PHILADELPHIA, PA.
DIVISION OF MERCK & CO., INC.

SD4058-P 658 Ph. 193100 Printed in U.S.A.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 010104

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MERCK SHARP & DOHME / RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC. WEST POINT, PENNSYLVANIA

File + NDA 8/15/56

August 9, 1956

New Drug Branch
Division of Medicine
Food and Drug Administration
Department of Health, Education,
and Welfare
Washington 25, D.C.

Gentlemen:

Re: 'Mephyton' Compressed Tablets
NDA 10104

Enclosed are five copies of printed label, carton, and basic circular for 'Mephyton' Compressed Tablets. Under separate cover we are sending you three market packages of this product (Fin. No. N6720). This is to complete your files on this subject.

Thank you for your continuing courtesy and cooperation.

Very truly yours,

Henry S. Thomas

Henry S. Thomas, M.D.
Director, Medical Services

HST/egm
Enclosure

INTRA-ADMINISTRATIVE REFERRAL

Issuance Date 8/12/55

Jacket Identification, Type and Number

NDA - 8448

To	Referrals and Recommendations
Division of Nutrition	Comment. NDA 8448 is attached in case you wish to refer to it. RLS Thank you The only problem that needs consideration is proper dosage. It seems to me that directions for use are adequate for safety. E M Nelson

This form to be used in lieu of yellow Agency Route Slip when requesting comments or recommendations.
Division name only to be used in "To" column. If individual is to be designated, indicate name in body of form to right of division.
Draw double line under conclusion of individual's dated recommendation.

FD-49

MERCK & CO., INC.
CHEMICAL DIVISION
RAHWAY, NEW JERSEY

August 1, 1955

Commissioner
Food and Drug Administration
Department of Health, Education,
and Welfare
Washington 25, D. C.

Gentlemen:

We are writing in connection with our new drug application for Emulsion of Vitamin K_1 (NDA 8448).

As a supplement to this application, we are attaching, in duplicate, pertinent data to support the oral use of this vitamin in tablet form. The clinical usefulness of this tablet is similar to that of the emulsion product.

Your early consideration of this application would be appreciated.

Very truly yours,

MERCK & CO., Inc.

J. M. Young
Chemical Control Division

JMY:moc

Attach.

Form FD-356
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Food and Drug Administration

Original ☐ or Supplemental ☒ Application

Name of applicant MERCK & CO., Inc.

Address Rahway, New Jersey

Date August 1, 1955

Name of new drug Vitamin K_1 Tablets
5 mg. Each

DO NOT USE THIS SPACE

NDA No. 10104

Received 8-3-55

Filed

Applicant notified

(If this is a supplemental application, see Item (8) on page 2)

To the SECRETARY, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Washington 25, D. C.

DEAR SIR:

The undersigned, MERCK & CO., Inc., submits this application with respect to a new drug pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. Attached hereto, in duplicate, and constituting a part of this application are the following:

(1) Full reports of all investigations which have been made to show whether or not the drug is safe for use.

(These reports should include, where necessary, detailed data derived from appropriate animal or other biological experiments in which the methods used and the results obtained are clearly set forth. Furthermore, reports of all clinical tests by experts, qualified by scientific training and experience to evaluate the safety of drugs, should be attached and should include detailed information pertaining to each person treated including age, sex, conditions treated, dosage, frequency of administration, duration of administration of the drug, results of clinical and laboratory examinations made, and a full statement of any adverse effects and therapeutic results observed.)

(2) A full list of the articles used as components of the drug.

(This list should include all substances used in the synthesis, extraction, or other method of preparation of the drug regardless of whether they undergo chemical change in the process.)

(3) A full statement of the composition of the drug.

(This statement should set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed.)

(4) (*a*) A full description of the methods used in the manufacture, processing, and packing of the drug.

(*b*) A full description of the facilities and controls used for the manufacture, processing, and packing of the drug.

(Included in this description should be information, when applicable, on the following:

(i) Precautions to insure proper identity, strength, and purity of the raw materials, including the specifications for acceptance of each lot of raw material.

(ii) Whether or not each lot of raw materials is given a serial number to identify it and the use made of such numbers in subsequent plant operations.

(iii) Method of preparation of formula card and manner in which it is used.

(iv) Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

(v) Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and at what stage and by whom this is done.

(vi) Precautions to check the total number of finished packages produced from a batch of the drug with the theoretical yield.

(vii) Precautions to insure that the proper labels are placed on the drug for a particular lot.

(viii) The analytical controls used during the various stages of the manufacturing, processing, and packing of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. If the article is one which is represented as sterile, the same information should be given for sterility controls. Include the specifications required for acceptance of each lot of the finished drug.

(ix) An explanation of the exact significance of any control numbers used in the manufacturing, processing, and packing of the drug, including any code numbers which may appear on the label of the finished article. State whether or not any of the numbers appear on invoices.

(x) Additional procedures employed which are designed to prevent contamination and otherwise insure proper control of the product.)

(5) One complete unit or package of the drug.

(If for any reason it is not practicable to submit such unit with the application, the reason should be stated. In case the drug is available only in limited quantity, a statement should also be made as to the extent to which samples of the drug and of the articles used as components of it will be available if requested by the Administrator.)

(6) Five copies of each label and other labeling to be used for the drug.

(Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package. The labeling should contain a statement of all the conditions under which the drug is to be used; or the label should identify specifically a brochure or other printed matter containing adequate directions for use, by physicians, dentists, or veterinarians, as the case may be, under all conditions under which the drug is to be used.)

(7) The drug is (or is not) to be exempt under regulation 1.106(b) or (c) as amended from the requirement of section 502(f)(1) of the Act that its labeling bear adequate directions for use.

(If the drug is to be so exempt, five copies of a brochure or other printed matter containing adequate directions for use under all conditions under which the drug is to be used should be attached, and a statement should be made showing that such brochure or other printed matter is readily available to physicians, dentists, or veterinarians, or if not that it is to be made so available upon the application's becoming effective. If the drug is to be so exempt, the labels, submitted with the application, should state that the brochure or other printed matter is available to physicians, dentists, or veterinarians upon request.)

(8) If this is a supplemental application, full information on each proposed change concerning any statement made in the effective application.

(After an application has become effective, a supplemental application should be filed setting forth any proposed change in the conditions under which the drug is to be used, in the labeling thereof, in any circumstance relating to its production, or in any other information contained in the effective application. The supplemental application may omit statements made in the effective application concerning which no change is proposed.)

Very truly yours,

MERCK & CO., Inc.
(Applicant)

Per B. L. Clarke

B. L. Clarke

Director of Chemical Control
(Indicate authority)

This application must be signed by the applicant or by his attorney or agent or, if a corporation, by an authorized official.

The data specified under the several numbered headings should be on separate sheets or sets of sheets, suitably identified. The sample of the drug, if sent under separate cover, should be properly identified on the outside of the shipping package.

The applicant will be notified of the date on which his application is filed. An incomplete application will not be filed but the applicant will be notified in what respect his application is incomplete.

ALL APPLICATIONS SHOULD BE SUBMITTED IN DUPLICATE
SINGLE COPIES WILL NOT BE ACCEPTED FOR FILING

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 010104

Post-approval DESI Review and FR Notice

LOG NO. 789

MEPHYTON

NATIONAL ACADEMY OF SCIENCES—NATIONAL RESEARCH COUNCIL
Division of Medical Sciences

DRUG EFFICACY STUDY

789

Form A

(To be submitted in duplicate by applicant)

1. NDA Number 10-104 2. Date Originally Approved 9/30/55 3. Rx [X] OTC [ ]

4. Brand Name Tablets Mephyton®

5. Applicant's Name Merck & Co., Inc.

and Address Rahway, N. J. 07065

6. Quantitative Formula

Established (Non-Proprietary) Name of Active Ingredients (in order shown on label)	Amount (per tablet, per ml., etc.)
Phytonadione (U.S.P.)	5 mg. per tablet

7. Dosage Form (tablets, etc.) Tablets

8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Oral

9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).

A set of pub. papers

Blue copy is original
White copy is duplicate

The back of this form may be used if additional space is needed.

Tablets Mephyton®

NDA No.
10-104

PROTHROMBIN DEFICIENCY

References:

1. Hill, J. M., Speer, R. J., Roberts, A. and Maloney, M.: Hypoprothrombinemia and hypoproconvertinemia during pregnancy, J. Lab. & Clin Med. 45: 308-312, Feb. 1955.

2. Cosgriff, S. W.: The effectiveness of an oral vitamin K_1 in controlling excessive hypoprothrombinemia during anticoagulant therapy, Ann. Int. Med. 45: 14-22, July 1956.

3. Haden, H. T.: Vitamin K deficiency associated with prolonged antibiotic administration, Arch. Int. Med. 100: 986-988, Dec. 1957.

4. Asteriadou-Samartzis, E. and Leikin, S.: The relation of vitamin K to hyperbilirubinemia, Pediatrics 21: 397-402, 1958.

5. Schirger, A., Spittal, J. A. and Ragen, P. A.: Small doses of vitamin K_1 for correction of reduced prothrombin activity, Proc. Staff Meet. Mayo Clin. 34: 453-458, Sept. 16, 1959.

6. Shaw, S.: Idiopathic steatorrhoea and haemorrhage due to malabsorption of vitamin K, Brit. M. J. 2: 647-648, Aug. 27, 1960.

7. Shoshkes, M., Willner, M., Pontoriero, G. and Chiong, R.: "Solubilized" vitamin K_1 (phytonadione) in neonatal hypoprothrombinemia, J. Pediat. 58: 27-31, Jan. 1961.

8. Vietti, T. J., Stephens, J. C. and Bennett, K. K.: Vitamin K_1 prophylaxis in the newborn, J.A.M.A. 176: 791-793, June 3, 1961.

9. Shoshkes, M., Rothfeld, E. L. and Jacobs, M.: Colloidally suspended phytonadione in bishydroxycoumarin-induced hypoprothrombinemia, Am. J. Cardiol. 8: 72-75, July 1961 (in Report on Therapy).

10. Weaver, W. T., Anlyan, W. G. and Postlethwait, R. W.: Blood coagulation factors in liver disease, Surgery 50: 207-212, July 1961.

11. Weiner, M. and Farhangi, M.: The response of hypoprothrombinemia in cirrhosis to vitamin K_1 and K_3, Am. J. Med. Sc. 242: 207-210, Aug. 1961.

12. Wafring, K. W.: Hemorrhage in the newborn and vitamin K prophylaxis, J. Pediat. 61: 686-692, Nov. 1962.

13. Ballard, H. S. and Marcus, A. J.: Decompensated portal cirrhosis, Arch. Int. Med. 117: 182-186, Feb. 1966.

No Package Insert

MEPHYTON
NDA 10104
LOG 789

Panel on Drugs Used in Hematologic Disorders

INDICATIONS

I. Anticoagulant-induced prothrombin deficiency.

EVALUATION: Effective.

COMMENTS: Vitamin K_1 has been known as an effective antidote to coumarin-like drugs for almost 20 years and is now among the agents of choice.

DOCUMENTATION:
1. James, D. F., I. L. Bennett, Jr., P. Scheinberg, and J. J. Butler. Clinical studies on dicumarol hypoprothrombinemia and vitamin K preparations. I. Superiority of vitamin K_1 oxide over menadione sodium bisulfite U.S.P. and synkayvite in reversing dicumarol hypoprothrombinemia. Arch. Intern. Med. 83:632-652, 1949.

II. Prophylaxis and therapy of hemorrhagic disease of the newborn.

EVALUATION: Effective, but . . . .

COMMENTS: When hemorrhagic disease of the newborn is due to vitamin K deficiency, vitamin K_1 is safe and effective. However, only small doses are required and the "up to 10 mg" recommended are probably excessive (1). The dose should not be repeated, for failure to respond implies a different diagnosis.

Clinical evidence is suggestive that vitamin K prophylaxis in the mother is effective in preventing hemorrhagic disease of the newborn (2).

DOCUMENTATION:
1. Aballi, A. J., V. L. Banus, S. de Lamerens, and S. Rosengvaig. Coagulation studies in the newborn period. III. Hemorrhagic disease of the newborn. A.M.A. J. Dis. Child. 97:524-548, 1959.
2. Stefanini, M., and W. Dameshek. Diseases due to deficiency of factors participating in the blood coagulation mechanism, pp. 247-307. In The Hemorrhagic Disorders. (2nd ed.) New York: Grune & Stratton, Inc., 1962.

III. Maternal hemorrhage due to hypoprothrombinemia.

EVALUATION: Ineffective.

COMMENTS: This indication is too vague. The usual type of maternal hemorrhage with a long "prothrombin time" is probably due to defibrination, which will not respond to vitamin K. The use of vitamin K in this obstetric emergency typically postpones proper diagnosis and appropriate treatment.

DOCUMENTATION:
1. Verstraete, M., C. Vermylen, J. Vermylen, and J. Vandenbroucke. Excessive consumption of blood coagulation components as cause of hemorrhagic diathesis. Amer. J. Med. 38:899-908, 1965.

IV. Presurgical use when hypoprothrombinemia is present or suspected.

EVALUATION: Ineffective.

COMMENTS: This is too vague, when applied to patients not on known drug therapy. Most such prolongation of prothrombin time will not represent vitamin K deficiency.

DOCUMENTATION:
1. Informed judgment and opinion of the Panel.

V. Hypoprothrombinemia due to other causes, including factors limiting absorption, inhibition, or destruction of vitamin K, e.g., obstructive jaundice and biliary fistula.

EVALUATION: Ineffective.

COMMENTS: Water-soluble vitamin K orally or any vitamin K preparation parenterally are required to correct these conditions. This response has long been common knowledge.

DOCUMENTATION:
1. Cohn, V. H., and H. G. Mandel. Fat-soluble vitamins. II. Vitamin K and vitamin E, pp. 1697-1706. In L. S. Goodman and A. Gilman, Eds. The Pharmacological Basis of Therapeutics. (3rd ed.) New York: The Macmillan Co., 1965.

VI. Hypoprothrombinemia due to sprue, ulcerative colitis, celiac disease, or intestinal resection.

EVALUATION: Ineffective.

COMMENTS: Intestinal malabsorption syndromes are well-known sources of vitamin K deficiency, but only the parenteral preparations are effective in these disorders.

DOCUMENTATION:
1. Spaet, T. H., and M. Kropatkin. Studies on "prothrombin derivatives" in vitamin K deficiency. Arch. Intern. Med. 102:558-561, 1958.

VII. Hypoprothrombinemia due to antibacterial therapy.

EVALUATION: Effective.

COMMENTS: Evidently, at least part of the human vitamin K requirement is met by synthesis in the gut by bacteria. Often patients in this category have a deficient diet as well.

DOCUMENTATION:
1. Cohn, V. H., and H. G. Mandel. Fat-soluble vitamins. II. Vitamin K and vitamin E, pp. 1697-1706. In L. S. Goodman and A. Gilman, Eds. The Pharmacological Basis of Therapeutics. (3rd ed.) New York: The Macmillan Co., 1965.

VIII. Hypoprothrombinemia due to drug administration.

EVALUATION: Ineffective.

COMMENTS: Unless a drug specifically affects vitamin K metabolism, vitamin K therapy will be ineffective. Streptokinase may (for example) produce a prolonged prothrombin time unaffected by vitamin K.

DOCUMENTATION:
1. Informed judgment and opinion of the Panel.

IX. Hepatic disease, with prothrombin deficiency.

EVALUATION: Ineffective.

COMMENTS: In parenchymatous liver disease vitamin K stores are typically adequate. The use of vitamin K preparations in this group of disorders may actually worsen the clotting defect. Documentation should be provided that slight improvement of the prothrombin time lessens the danger of serious hemorrhage.

MEPHYTON
NDA 10104
LOG 789

DOCUMENTATION:

1. Unger, P. N., and S. Shapiro. The prothrombin response to the parenteral administration of large doses of vitamin K in subjects with normal liver function and in cases of liver disease: a standardized test for the estimation of hepatic function. J. Clin. Invest. 27:39-47, 1948.

GENERAL COMMENTS

Different spectrums of clinical activity exist for the various vitamin K preparations (lipid-soluble vs. water-soluble) and routes of administration (oral vs. parenteral). For this reason the Panel recommends that oral and parenteral vitamin K preparations not be incorporated into one package insert.

General Statement on the Use of Vitamin K Preparations for Hypoprothrombinemia.

The physiologic function of vitamin K is related to the hepatic biosynthesis of clotting factors II, VII, IX, and X. The chief clinical manifestation of vitamin K deficiency is an increased bleeding tendency most commonly detected by demonstration of increased prothrombin time.

Menadione and natural vitamin K are lipid-soluble substances, but active water-soluble derivatives of menadione may be prepared by forming the sodium bisulfite salt or the tetrasodium salt of the diphosphoric acid ester. These lipid-soluble and water-soluble vitamin K preparations have different spectrums of clinical activity. For this reason, oral (lipid-soluble or water-soluble) and parenteral preparations should not be incorporated in a common package insert.

Hypoprothrombinemia may be associated with prolonged biliary fistula and intrahepatic or extrahepatic biliary obstruction because the lipid-soluble vitamin is poorly absorbed in the absence of bile. Parenteral therapy, oral water-soluble preparations, or oral fat-soluble preparations with concomitantly administered bile salts are required in this condition. Hypoprothrombinemia following hepatocellular disease is usually not favorably influenced, and in fact may be further augmented by the administration of vitamin K (6). The response of hypoprothrombinemia to parenteral vitamin K administration has been used as a test to distinguish between jaundice due to obstruction and that due to hepatocellular disease, although this test may now be outdated.

Hypoprothrombinemia secondary to disorders of intestinal absorption, such as sprue, cystic fibrosis of the pancreas, regional enteritis, ulcerative colitis, gastrointestinal fistula, and extensive bowel resection, should be treated with parenteral vitamin K preparations (4).

Hypoprothrombinemia arising from a purely dietary deficiency of vitamin K is probably never seen. Not only is the vitamin present in many foods, but it is synthesized by intestinal bacteria (1). The presence of almost complete dietary restriction combined with antibiotic sterilization of the intestinal tract may lead to vitamin K deficiency. Either oral or parenteral vitamin K preparations may be administered to correct the ensuing deficiency.

The newborn normally has low levels of vitamin K-dependent clotting factors. These may be further depressed and accompanied by hemorrhagic manifestations in rare cases. Vitamin K, given prophylactically to the mother (5) or to the afflicted infant, will probably reverse this abnormality. It should be noted, however, that most hemorrhagic disease in the newborn is not a result of vitamin K deficiency. The use of water-soluble or synthetic vitamin K derivatives, reported to produce hemolytic anemia, hyperbilirubinemia, and kernicterus in the newborn, especially in premature infants, is not recommended (2).

Drug-induced hypoprothrombinemia following the use of vitamin K antagonists should be treated with the fat-soluble or natural vitamin K preparation, and not the synthetic vitamin K preparations, which are considerably less effective for this purpose (3).

DOCUMENTATION:

1. Cohn, V. H., and H. G. Mandel. Fat-soluble vitamins. II. Vitamin K and vitamin E, pp. 1697-1706. In L. S. Goodman and A. Gilman, Eds. The Pharmacological Basis of Therapeutics. (3rd ed.) New York: The Macmillan Co., 1965.
2. Dyggve, H. Bilirubin studies in premature infants who received menadione derivatives or vitamin K_1 at birth. Acta Paediat. 49:230-242, 1960.
3. James, D. F., I. L. Bennett, Jr., P. Scheinberg, and J. J. Butler. Clinical studies on dicumarol hypoprothrombinemia and vitamin K preparations. I. Superiority of vitamin K_1 oxide over menadione sodium bisulfite U.S.P. and synkayvite in reversing dicumarol hypoprothrombinemia. Arch. Intern. Med. 83:632-652, 1949.
4. Spaet, T. H., and M. Kropatkin. Studies on "prothrombin derivatives" in vitamin K deficiency. Arch. Intern. Med. 102:558-561, 1958.
5. Stefanini, M., and W. Dameshek. Diseases due to deficiency of factors participating in the blood coagulation mechanism, pp. 247-307. In The Hemorrhagic Disorders. (2nd ed.) New York: Grune & Stratton, Inc., 1962.
6. Unger, P. N., and S. Shapiro. The prothrombin response to the parenteral administration of large doses of vitamin K in subjects with normal liver function and in cases of liver disease: a standardized test for the estimation of hepatic function. J. Clin. Invest. 27:39-47, 1948.

Approved by _____

Chairman

methods, facilities, and controls, in accordance with the requirements of section 512 of the act.

Written comments regarding this announcement, including requests for an informal conference, may be addressed to the Bureau of Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852.

The manufacturer of the listed drug has been mailed a copy of the NAS–NRC report. Any other interested person may also obtain a copy by writing to the Food and Drug Administration, Press Relations Staff, 200 C Street SW., Washington, D.C. 20204.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 512, 52 Stat. 1050–51, 82 Stat. 343–51; 21 U.S.C. 352, 360b) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: July 24, 1970.

SAM D. FINE,
Associate Commissioner for Compliance.

[F.R. Doc. 70-11141; Filed, Aug. 24, 1970; 8:46 a.m.]

[DESI 0151NV]

PENICILLIN, STREPTOMYCIN, AND VITAMIN PREPARATION

Drugs for Veterinary Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on Medic-Aid 2–50 Soluble; each pound contains 10 million units penicillin (from procaine penicillin), 30 million units penicillin (from potassium penicillin), 120 grams streptomycin sulfate, 6 million units vitamin A, 4 million I.C. units vitamin D, and 4 grams of vitamin K (menadione sodium bilsulfite); marketed by Salsbury Laboratories, Charles City, Iowa 50616.

The Academy evaluated this preparation as probably not effective for use in drinking water against bacterial infections of poultry, swine, and calves.

The Academy stated:

1. Each disease claim should be properly qualified as "appropriate for use in (name of disease) caused by pathogens sensitive to (name of drug)." If the disease cannot be so qualified, the claim must be dropped.

2. Claims made "for prevention of" or "to prevent" should be replaced with "as an aid in the control of" or "to aid in the control of".

3. Substantial evidence was not presented to establish that each ingredient designated as active makes a contribution to the total effect claimed for the drug combination.

4. The label should warn that treated animals must actually consume enough medicated water to provide a therapeutic dose under the conditions that prevail, and as a precaution state the desired amount of drug per unit of animal weight per day for each species as a guide to effective use of the preparation in drinking water.

5. The disease claims for streptomycin sulfate in this preparation must be restricted to diseases involving the gastrointestinal tract because of the chemical and pharmacological properties of streptomycin sulfate.

6. Penicillin doses recommended are too low.

The Food and Drug Administration concurs in the Academy's evaluation.

This evaluation is concerned only with the drug's effectiveness and safety to the animal to which administered. It does not take into account the safety for food use of food derived from drug-treated animals. Nothing herein will constitute a bar to further proceedings with respect to questions of safety of the drug or its metabolites as residues in food products derived from treated animals.

This announcement is published (1) to inform the holders of new animal drug applications of the findings of the Academy and the Food and Drug Administration and (2) to inform all interested persons that such articles to be marketed must be the subject of approved new animal drug applications and otherwise comply with all other requirements of the Federal Food, Drug, and Cosmetic Act.

Holders of new animal drug applications are provided 6 months from the date of publication of this announcement in the FEDERAL REGISTER to submit adequate documentation in support of the labeling used.

Each holder of a "deemed approved" new animal drug application (i.e., an application which became effective on the basis of safety prior to Oct. 10, 1962) for such drugs is requested to submit updating information as needed to make the application current with regard to manufacture of the drug, including information on drug components and composition, and also including information regarding manufacturing methods, facilities, and controls, in accordance with the requirements of section 512 of the act.

Written comments regarding this announcement, including requests for an informal conference, may be addressed to the Bureau of Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852.

The holder of the new animal drug application for the listed drug has been mailed a copy of the NAS–NRC report. Any manufacturer, packer, or distributor of a drug of similar composition and labeling to the listed drug or any other interested person may obtain a copy by writing to the Food and Drug Administration, Press Relations Staff, 200 C Street SW., Washington, D.C. 20204.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 512, 52 Stat. 1050–51, 82 Stat. 343–51; 21 U.S.C. 352, 360b) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: July 7, 1970.

SAM D. FINE,
Acting Associate Commissioner for Compliance.

[F.R. Doc. 70-11142; Filed, Aug. 24, 1970; 8:46 a.m.]

[DESI 2139]

[Docket No. FDC-D-218; NDA 2-139 et al.]

MENADIOL SODIUM DIPHOSPHATE, MENADIONE SODIUM BISULFATE, MENADIONE, AND PHYTONADIONE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drugs:

1. a. Menadiol sodium diphosphate; marketed as Synkayvite Ampuls by Roche Laboratories, Division of Hoffman-LaRoche, Inc., 340 Kingsland Avenue, Nutley, N.J. 07110 (NDA 3-718).

b. Menadiol sodium diphosphate; marketed as Synkayvite Tablets by Roche Laboratories, Division of Hoffman-LaRoche, Inc. (NDA 3-718).

2. Phytonadione; marketed as Konakion Injectable by Roche Laboratories, Division of Hoffman-LaRoche, Inc. (NDA 11-745).

3. Phytonadione; marketed as Aquamephyton Injection by Merck Sharp & Dohme, Division of Merck and Company, Inc., Rahway, N.J. 07065 (NDA 12-223).

4. Phytonadione; marketed as Mephyton Tablets by Merck Sharp & Dohme, Division of Merck & Co., Inc. (NDA 10-104).

5. a. Menadione sodium bisulfite marketed as Hykinone Tablets by Abbott Laboratories, 14th Street and Sheridan Road, North Chicago, Ill. 60064 (NDA 2-694).

b. Menadione sodium bisulfite; marketed as Hykinone Injection by Abbott Laboratories (NDA 2-694).

6. Menadiol sodium diphosphate; marketed as Kappadione Injection by Eli Lilly and Co., Inc., Post Office Box 618, Indianapolis, Ind. 46206 (NDA 5-725).

7. Menadione Tablets; marketed by Eli Lilly & Co., Inc. (NDA 2-139).

The 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. A new-drug application is required from any person marketing such drugs without approval.

The Food and Drug Administration is prepared to approve new-drug applications and supplements to previously approved new-drug applications under conditions described in this announcement.

I. *Menadiol sodium diphosphate; menadione sodium bisulfite; menadione*

for oral administration.—A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy reports, as well as other available evidence, and concludes that:

1. a. Menadiol sodium diphosphate, menadione sodium bisulfite, and menadione are effective for use in the indications stated in the labeling conditions in paragraph IC.

b. Although these drugs may be effective in preventing hemorrhagic disease of the newborn, the risks associated with such use do not justify administration to the newborn or to the mother during the last weeks of pregnancy.

2. There is a lack of substantial evidence of effectiveness for the following indications which appear in the labeling of one or more of these drugs: Hypoprothrombinemia secondary to impaired absorption from gastrointestinal fistulas, ulcerative colitis, and conditions associated with steatorrhea, such as sprue, celiac disease, and cystic fibrosis of the pancreas; after the administration of large doses of quinine; after the administration of prothrombin-depressing drugs, such as barbiturates; prevention of secondary hemorrhage after tonsillectomy; liver disease; anticoagulant-induced hypoprothrombinemia; and prophylaxis in surgery.

B. *Form of drug.* These preparations are in tablet form suitable for oral administration.

C. *Labeling conditions.* 1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations. Its labeling bears adequate information for safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970. The "Indications" section is as follows: (Labeling guidelines for the drug are available from the Administration on request.)

INDICATIONS

Vitamin K deficiency secondary to the administration of antibacterial therapy.

Hypoprothrombiemia secondary to obstructive jaundice and biliary fistulas. Bile salts must be administered concomitantly. Menadione is ineffective alone. The menadiol salts may be effective alone.

Hypoprothrombinemia secondary to administration of salicylates.

II. *Menadiol sodium diphosphate and menadione sodium bisulfite injection.*—A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy reports, as well as other available evidence, and concludes that:

1. a. Menadiol sodium diphosphate and menadione sodium bisulfite injection are effective for the indications stated in the labeling conditions in paragraph IIC. These drugs are also effective for use as a liver function test. This use does not now appear in the indications in paragraph C, as such use is now probably archaic; however, it may be included in the labeling with properly qualifying comments.

b. Although menadiol sodium diphosphate and menadione sodium bisulfite injection may be effective in preventing hemorrhagic disease of the newborn, the risks associated with use of these drugs in the newborn do not justify administration to the newborn or to the mother during the last few weeks of pregnancy.

2. There is a lack of substantial evidence that menadiol sodium diphosphate and menadione sodium bisulfite injection are effective for the following indications for which one or both drugs are recommended: Hypoprothrombinemia secondary to the administration of large doses of quinine; after administration of prothrombin-depressing drugs, such as barbiturates; prevention of secondary hemorrhage after tonsillectomy; liver disease; anticoagulant-induced hypoprothrombinemia; prophylaxis in surgery; impaired liver function massive hemorrhage; and cirrhosis of the liver, toxic and infectious hepatitis, acute yellow atrophy and neoplasms of this organ.

B. *Form of drug.* These preparations are sterile solutions suitable for parenteral administration.

C. *Labeling conditions.* 1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations. Its labeling bears adequate information for safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970. The "Indications" section is as follows: (Labeling guidelines for the drug are available from the Administration on request.)

INDICATIONS

Hypoprothrombinemia secondary to factors limiting absorption of synthesis of vitamin K, e.g., obstructive jaundice, biliary fistula, sprue, ulcerative colitis, celiac disease, intestinal resection, cystic fibrosis of the pancreas, regional enteritis, and antibacterial therapy.

Hypoprothrombinemia secondary to administration of salicylates.

III. *Phytonadione for oral administration*—A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy reports, as well as other available evidence, and concludes that the drug:

1. Is effective for the indications stated in the labeling conditions in paragraph III.C.

2. Lacks substantial evidence of effectiveness for its recommended use for: maternal hemorrhage due to hypoprothrombinemia; hypoprothrombinemia due to drug administration; hepatic disease, with prothrombin deficiency; presurgical use when hypoprothrombinemia is present or suspected; and hypoprothrombinemia due to other causes, including factors limiting absorption, inhibition, or destruction of vitamin K, e.g., obstructive jaundice and biliary fistula.

B. *Form of drug.* Phytonadione preparations are in tablet form suitable for oral use.

C. *Labeling conditions.* 1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations. Its labeling bears adequate information for safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970. The "Indications" section is as follows: (Labeling guidelines for the drug are available from the Administration on request.)

INDICATIONS

Anticoagulant-induced prothrombin deficiency.

Hypoprothrombinemia secondary to antibacterial therapy.

Hypoprothrombinemia secondary to administration of salicylates.

Hypoprothrombinemia secondary to obstructive jaundice or biliary fistulas. Bile salts are administered concurrently.

IV. *Phytonadione injection*—A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy reports, as well as other available evidence, and concludes that:

1. Phytonadione injection is effective for the indications stated in the labeling conditions in paragraph IV.C.

2. Phytonadione injection lacks substantial evidence of effectiveness for its recommended use for: maternal hemorrhage due to hypoprothrombinemia; presurgical use when hypoprothrombinemia is present or suspected; hypoprothrombinemia due to drug administration; hepatic disease with prothrombin deficiency; low prothrombin values incident to barbiturates; low prothrombin values incident to other prothrombin-depressing drugs; severe liver disease; and prevention of excessive bleeding due to hypoprothrombinemia in surgical procedures (biliary tract surgery, tonsillectomy and other operations in highly vascular areas, surgery on jaundiced patients, etc.).

B. *Form of drug.* These preparations are sterile solutions suitable for parenteral administration.

C. *Labeling conditions.* 1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations. Its labeling bears adequate information for safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970. The "Indications" section is as follows: (Labeling guidelines for the drug are available from the Administration on request.)

INDICATIONS

Anticoagulant-induced prothrombin deficiency.

Prophylaxis and therapy of hemorrhagic disease of the newborn.

Hypoprothrombinemia due to antibacterial therapy.

Hypoprothrombinemia secondary to factors limiting absorption or synthesis of vitamin K, e.g., obstructive jaundice, biliary fistula, sprue, ulcerative colitis, celiac disease,

intestinal resection, cystic fibrosis of the pancreas, and regional enteritis.

Other drug-induced hypoprothrombinemia where it is definitely shown that the result is due to interference with vitamin K metabolism, e.g., salicylates.

V. *Marketing status.* Marketing of the drugs may continue under the conditions described in items VI and VII of this announcement.

VI. *Previously approved applications.* 1. Each holder of a "deemed approved" new-drug application (i.e., an application which became effective on the basis of safety prior to Oct. 10, 1962) for such drug is requested to seek approval of the claims of effectiveness and bring the application into conformance by submitting supplements containing:

a. Revised labeling as needed to conform to the labeling conditions described here for the drug and complete current container labeling, unless recently submitted.

b. Adequate data to assure the biologic availability of the drug in the formulation which is marketed. If such data are already included in the application, specific reference thereto may be made.

c. Updating information as needed to make the application current in regard to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of the new-drug application form FD-356H to the extent described for abbreviated new-drug applications, § 130.4(f), published in the FEDERAL REGISTER April 24, 1970 (35 F.R. 6574). (One supplement may contain all the information described in this paragraph.)

2. Such supplements should be submitted within the following periods after the date of publication of this notice in the FEDERAL REGISTER:

a. 60 days for revised labeling—the supplement should be submitted under the provisions of § 130.9 (d) and (e) of the new-drug regulations (21 CFR 130.9) which permit certain changes to be put into effect at the earliest possible time.

b. 180 days for biologic availability data.

c. 60 days for updating information.

3. Marketing of the drug may continue until the supplemental applications submitted in accord with the preceding subparagraphs 1 and 2 are acted upon, provided that within 60 days after the date of this publication, the labeling of the preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described in this announcement.

VII. *New applications.* 1. Any other person who distributes or intends to distribute such drug which is intended for the conditions of use for which it has been shown to be effective, as described under A above, should submit an abbreviated new-drug application meeting the conditions specified in § 130.4(f) (1), (2), and (3), published in the FEDERAL REGISTER of April 24, 1970 (35 F.R. 6574). Such applications should include proposed labeling which is in accord with the labeling conditions described herein and adequate data to assure the biologic availability of the drug in the formulation which is marketed or proposed for marketing.

2. Distribution of any such preparation currently on the market without an approved new-drug application may be continued provided that:

a. Within 60 days from the date of publication of this announcement in the FEDERAL REGISTER, the labeling of such preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described herein.

b. The manufacturer, packer, or distributor of such drug submits, within 180 days from the date of this publication, a new-drug application to the Food and Drug Administration.

c. The applicant submits within a reasonable time additional informaton that may be required for the approval of the application as specified in written communications from the Food and Drug Administration.

d. The application has not been ruled incomplete or unapprovable.

VIII. *Exemption from periodic reporting.* The periodic reporting requirements of §§ 130.35(e) and 130.13(b)(4) are waived in regard to applications approved for these drugs. The requirements of §§ 130.35(f) and 130.13(b) (1), (2), and (3) remain a continuing responsibility of each applicant.

IX. *Opportunity for a hearing.* 1. The Commissioner of Food and Drugs proposes to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act withdrawing approval of all new-drug applications and all amendments and supplements thereto providing for the indications for which substantial evidence of effectiveness is lacking as described in paragraphs I.A.2, II.A.2, III.A.2, and IV.A.2, of this announcement. An order withdrawing approval of the applications will not issue if such applications are supplemented, in accord with this notice, to delete such indications. Promulgation of the proposed order would cause any drug for human use containing the same components and offered for the indications for which substantial evidence of effectiveness is lacking, to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

2. In accordance with the provisions of section 505 of the Act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the holders of any such applications, and any interested person who would be adversely affected by such an order, an opportunity for a hearing to show why such indications should not be deleted from labeling. A request for a hearing must be filed within 30 days after the date of publication of this notice in the FEDERAL REGISTER. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that a genuine and substantial issue of fact requires a hearing, together with a well-organized and full-factual analysis of the clinical and other investigational data the objector is prepared to prove in a hearing. Any data submitted in response to this notice must be previously unsubmitted and include data from adequate and well-controlled clinical investigations (identified for ready review) as described in § 130.12 (a)(5) of the regulations published in the FEDERAL REGISTER of May 8, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained under uncontrolled or partially controlled situations are not acceptable as a sole basis for approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety. If a hearing is requested and justified by the response to this notice, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence.

X. *Unapproved use or form of drug.* 1. If the article is labeled or advertised for use in any condition other than those provided for in this announcement, it may be regarded as an unapproved new drug subject to regulatory proceedings until such recommended use is approved in a new-drug application or is otherwise in accord with this announcement.

2. If the article is proposed for marketing in another form or for a use other than the use provided for in this announcement, appropriate additional information as described in § 130.4 or §130.9 of the regulations (21 CFR 130.4, 130.9) may be required, including results of animal and clinical tests intended to show whether the drug is safe and effective.

A copy of the NAS-NRC report has been furnished to each firm referred to above. Any other interested person may obtain a copy by request to the appropriate office named below.

Communications forwarded in response to this announcement should be identified with the reference number DESI 2139 and addressed (unless otherwise specified) to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Supplements (identify with NDA number): Office of Marketed Drugs (BD-200), Bureau of Drugs.

Original abbreviated new-drug applications (identify as such): Office of Marketed Drugs (BD-200), Bureau of Drugs.

Request for Hearing (identify with Docket Number): Hearing Clerk, Office of General Counsel (GC-1), Room 6-62, Parklawn.

All other communications regarding this announcement: Special Assistant for Drug Efficacy Study Implementation (BD-201), Bureau of Drugs.

Requests for NAS-NRC reports: Press Relations Office (CE-200), Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: July 17, 1970.

SAM D. FINE,
Associate Commissioner for Compliance.

[F.R. Doc. 70-11143; Filed, Aug. 24, 1970; 8:46 a.m.]