CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

87-955

Generic Name: Vitamin K₁

Sponsor: Abbott Laboratories

Approval Date: July 25, 1983
## CENTER FOR DRUG EVALUATION AND RESEARCH

### APPLICATION NUMBER:
87-955

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

87-955

APPROVAL LETTER
Abbott Laboratories
Attention: Mr. Frederic A. Gustafson
Abbott Park
North Chicago, IL 60064

Gentlemen:

Please refer to your new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act for Vitamin K1 (phytonadione) Injection, USP, 10 mg/ml in 1 ml ampul.

Reference is also made to your communication dated July 8, 1983.

We have completed the review of this abbreviated new drug application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

We have not yet completed our validation of the regulatory methods in this application; we therefore expect your continued cooperation to help resolve expeditiously any problems that may arise with respect to validation.

Any significant change in the conditions outlined in this abbreviated new drug application, requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.9 of the new drug regulations.

This Administration should be advised of any change in the marketing status of this drug.

The requirement for adequate data to assure the biologic availability is being deferred at the present time. However, our action in approving this application is based upon an understanding that if this requirement is reinstated you will perform the appropriate procedures.

For Initial Campaigns: We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Advertising and Labeling (HFN-240). Also, please do no use Form FD-2253 for this submission.

For Subsequent Campaigns: We call your attention to Regulation 21 CFR 310.300(b)(3) which requires that material for any subsequent advertising or promotional campaigns, at the time of their initial use, be submitted to our Division of Drug Advertising and Labeling (HFN-240) with a completed form FD-2253. A copy of Form FD-2253 is enclosed for your convenience.
The enclosures summarize the conditions relating to the approval of this application.

Appreciably yours,

[Signature]

[Date: 7/25/83]

Marvia Seife, M.D.
Director
Division of Generic Drug Monographs
Office of the Associate Director
for Drug Monographs
Office of Drugs
National Center for Drugs and Biologics

Enclosures:
Conditions of Approval of a New Drug Application
Records & Reports Requirements
Form FD-2253

cc: CHI-DO
HFN-530
HFN-616
HFN-5
HFN-313
DUP
-KJohnson/JLMeyer/CChang: 7-18-83
MSeife/djw: 7-19-83
Approval: 7-20-83

[Date: 7/20/83]
APPLICATION NUMBER:

87-955

Final Printed Labeling
Exhibit I

Final Printed Labeling
Vitamin K₁ Injection
PHYTONADIONE INJ., USP
Aqueous Colloidal Solution of Vitamin K₁
Ampul
FlipTop Vial

WARNING — INTRAVENOUS USE
Severe reactions, including fatalities, have occurred during and immediately after INTRAVENOUS injection of phyttonadione even when precautions have been taken to dilute the vitamin and avoid rapid infusion. Typically these severe reactions have resembled hypersensitivity or anaphylaxis, including "shock," "anaphylactic" and/or respiratory arrest. Some patients have exhibited these severe reactions on receiving phyttonadione for the first time. Therefore, the intravenous route should be restricted to those situations where other routes are not feasible and the serious risk involved is considered justified.

DESCRIPTION
Vitamin K₁ Injection (Phyttonadione Injection, USP) is a yellow, sterile, nonpyrogenic aqueous colloidal solution available for injection by the intravenous, intramuscular and subcutaneous routes. Each milliliter contains phyttonadione 2 or 10 mg, polyoxyethylene fatty acid derivative 70 mg, dextrose, hydrous 37.5 mg in water for injection; benzyl alcohol 9 mg added as preservative. May contain hydrochloric acid for pH adjustment. Approximate pH 6.
Phyttonadione, USP is chemically designated 2-methyl-3-(3,7,11,15-tetramethyl-2-hexadeceny)-1,4-naphthaledenedione, (C₂₁H₄₄O₂), a viscous liquid.
insoluble in water. It has the following structural formula:

Vitamin K. Injection (Phytonadione Injection, USP) aqueous colloidal solution for parenteral injection possesses the same type and degree of activity as does naturally-occurring vitamin K which is necessary for the production via the liver of active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor XI). The prothrombin test is sensitive to the levels of factors II, VII and X. The mechanism by which vitamin K promotes formation of these clotting factors in the liver is not known.

The action of the aqueous colloidal solution, when administered intravenously, is generally detectable within an hour or two, and hemorrhage is usually controlled within 3 to 6 hours. A normal prothrombin level may often be obtained in 12 to 14 hours.

In the prophylaxis and treatment of hemorrhagic disease of the newborn, phytonadione has demonstrated a greater margin of safety than that of the water soluble vitamin K analogues.

INDICATIONS
Vitamin K. Injection is indicated in the following coagulation disorders which are due to faulty formation of factors II, VII, IX and X when caused by vitamin K deficiency or interference with vitamin K activity.

Vitamin K. Injection is indicated in:
• 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, bilious fistula, sprue, ulcerative colitis, celiac disease, intestinal resection, cystic fibrosis of the pancreas and regional enteritis;
• Other drug-induced hypoprothrombinemias where it is definitely shown that the result is due to interference with vitamin K metabolism e.g., salicylates.

CONTRAINDICATION
Hypersensitivity to the drug or any ingredients in the formulation.

WARNINGS
See WARNINGS box.
Benzy alcohol acts as a preservative in Bacteriostatic Sodium Chloride Injection has been associated with toxicity in newborns. Data are unavailable on the toxicity of other preservatives in this age group. There is no evidence to suggest that the small amount of benzy alcohol contained in Phytonadione Injection, when used as recommended, is associated with toxicity.

Phytonadione promotes the synthesis of prothrombin by the liver and does not directly counteract the effects of the oral anticoagulants; it takes up to two hours for vitamin K to promote prothrombin synthesis. Whole blood or component therapy may also be required for severe blood loss. Phytonadione will not counteract the anticoagulant action of heparin.

When Vitamin K. Injection (Phytonadione Injection, USP) is used to correct excessive anticoagulant-induced hypoprothrombinemia, anticoagulant therapy should be continued. The patient is again faced with the clotting hazards existing prior to starting the anticoagulant therapy. Phytonadione is not a clotting agent, but overzealous therapy with vitamin K may restore conditions which originally permitted thromboembolic phenomena. Dosage should therefore be kept as low as possible, and prothrombin time should be checked regularly as clinical conditions indicate.

Repeated large doses of vitamin K are not warranted in liver disease, if the response to initial
use of the vitamin is unsatisfactory. Failure to respond to vitamin K may indicate the presence of a coagulation defect or that the condition being treated is unresponsive to vitamin K.

**PRECAUTIONS**

Store in a dark place, and protect from light at all times.

Temporary resistance to prothrombin-depressing anticoagulants may result, especially when larger doses of phytonadione are used. If relatively large doses have been employed, it may be necessary when reinstituting anticoagulant therapy to use somewhat larger doses of the prothrombin-depressing anticoagulant, or to use one which acts on a different principle, such as heparin sodium.

**Pregnancy Category C.** Animal reproduction studies have not been conducted with Vitamin K Injection. It is also not known whether Vitamin K Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Vitamin K injection should be given to a pregnant woman only if clearly needed.

**ADVERSE REACTIONS**

Deaths have occurred after intravenous administration. (See boxed WARNING statement on first page.)

Pain, swelling, and tenderness at the injection site may occur. The possibility of allergic sensitivity, including an anaphylactoid reaction, should be kept in mind.

Hyperbilirubinemia has been reported in the newborn, particularly in premature infants receiving doses above those recommended. This effect, with its possibility of attendant kernicterus, should be borne in mind if such dosages are deemed necessary.

Transient "flushing sensations" and "peculiar" sensations of taste have been observed as well as rare instances of dizziness, rapid and weak pulse, profuse sweating, brief hypotension, dyspnea and cyanosis. Rarely, after repeated injections, reactions resembling erythema perstans have been reported.

**DOSEAGE AND ADMINISTRATION**

Whenever possible, Vitamin K Injection (Phytonadione Injection, USP) should be given by the subcutaneous or intramuscular route. When intravenous administration is considered unavoidable, the drug should be injected very slowly, not exceeding 1 mg per minute.

The human minimum daily requirements for vitamin K have not been established officially, but they have been estimated to be 1 to 5 mcg/kg of body weight for infants and 0.03 mcg/kg for adults. Usually, the dietary abundance of vitamin K will satisfy these requirements, except during the first five to eight days of the neonatal period.

**Anticoagulant-Induced Prothrombin Deficiency**

To correct excessively prolonged prothrombin time caused by oral anticoagulant therapy—2.5 to 10 mg or up to 25 mg initially is recommended. In rare instances 50 mg may be required. Frequency and amount of subsequent doses should be determined by prothrombin time response or clinical condition. If in 6 to 8 hours after parenteral administration the prothrombin time has not been shortened satisfactorily, the dose should be repeated.

In the event of shock or excessive blood loss, the use of whole blood or component therapy is indicated.

Smaller doses are recommended for patients being treated with the shorter-acting anticoagulants, and for those in need of continued anticoagulant therapy. The smallest effective dose should be sought to obviate the possibility of temporary resistance to further anticoagulant therapy, and to avoid lowering the prothrombin time too far below that indicating an effective level of anticoagulant activity.

Larger doses are recommended for patients on the longer-acting anticoagulants, for those with severe bleeding, and for those not needing further anticoagulant therapy. Although more than 25 mg may be necessary, and a dose may be repeated, these courses of action are indicated only rarely.

**Prophylaxis and Treatment of Hemorrhagic Disease of the Newborn**

**Prophylaxis**

The Committee on Nutrition of the American Academy of Pediatrics recommends that vitamin K, be given to the newborn. A single intramuscular dose of phytonadione, 0.5 to 1.0 mg, is recommended. Although less desirable, phytonadione, 1 to 5 mg, may be given to the mother 12 to 24 hours before delivery.

**Treatment**

Phytonadione 1.0 mg should be given either subcutaneously or intramuscularly. Higher doses may be necessary if the mother has been receiving oral anticoagulants.

Empiric administration of vitamin K should not replace proper laboratory evaluation of the
coagulation mechanism. A prompt response (shortening of the prothrombin time in 2 to 4 hours) following administration of vitamin K, is usually diagnostic of hemorrhagic disease of the newborn, and failure to respond indicates another diagnosis or coagulation disorder.

Whole blood or component therapy may be indicated if bleeding is excessive. This therapy, however, does not correct the underlying disorder and phytonadione should be given concurrently.

**Hypoprothrombinemia Associated with Prolonged Hyperalimentation**

For prevention of hypoprothrombinemia associated with vitamin K deficiency in patients receiving total parenteral nutrition or prolonged hyperalimentation, it has been recommended that adults be given 5 to 10 mg of phytonadione intramuscularly once weekly, and children receive 2 to 5 mg intramuscularly once weekly. Infants who are breast fed or are receiving milk substitute formulas should be given 1 mg of phytonadione per month intramuscularly or subcutaneously, whenever the vitamin K content of the diet is below 100 mcg/ml.

**Hypoprothrombinemia Due to Other Causes**

A dosage of 2.5 to 25 mg or more (rarely up to 50 mg) is recommended, the amount and route of administration depending upon the severity of the condition and response obtained.

If possible, discontinuation or reduction of the dosage of drugs interfering with coagulation mechanisms (such as salicylates or antibiotics) is suggested as an alternative to administering concurrent phytonadione. The severity of the coagulation disorder should determine whether the immediate administration of phytonadione is required in addition to discontinuation or reduction of interfering drugs.

**Directions For Dilution**

Phytonadione may be diluted with 0.9% Sodium Chloride Injection, 5% Dextrose Injection or 5% Dextrose and Sodium Chloride Injection. Benzyl alcohol as a preservative has been associated with toxicity in newborns. Therefore, all of the above diluents should be preservative-free (See WARNINGS); other diluents should not be used. When dilutions are indicated, administration should be started immediately after mixture with the diluent, and unused portions of the dilution should be discarded, as well as unused contents of the container.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

87-955

CHEMISTRY REVIEW(S)
Statement Date: DESI 2139
NDA: 87-955

PROPOSED AMENDMENT/SUPPLEMENT
control & lab results

DEPARTMENT OF HEALTH

NAME: Abbott Labs. - N. Chicago 60064

PRESCRIPTION OF AMENDMENT/SUPPLEMENT

AMERICAN FAMILY

AMERICAN CATEGORY
Prothrombogenic vitamin

NAME OF DRUG
Phytonadione (Vitamin K1)

AGGREGATION
injection (aqueous colloidal)

POTENCY(IES)
10 mg/ml

AMOUNT
1 ml, type 1, amber ampul

PREPARATION AND MANUFACTURING

MANUFACTURING AND INSPECTION

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

ABILITY
protocol: satisfactory

EXP. DATE: 12 mo w/challenge data

MARKS AND NOTATION: 1

CHANGING APPROXIMATE: 7-20-83
CHEMIST'S REVIEW FOR
3BREVIA TED NEW DRUG APPLICATION
OR SUPPLEMENT

AMENDMENT ADDRESS OF APPLICANT
Abbott Labs. - N. Chicago 60064

PURPOSE OF AMENDMENT/SUPPLEMENT
control & lab results

HARMACOLOGICAL CATEGORY
Prothrombogenic vitamin

NAME OF DRUG
Phytonadione (Vitamin KL)

HOW DISPENSED
RX  XX  OTC

OSAGE FORM(S)
injection (aqueous colloidal

POTENCY(IES)
10 mg/ml

RELATED IND/NDA/DMF
87-955 10 mg/ml 1 ml ampul
87-954 2mg/ml 0.5 ml ampul
87-956 10 mg/ml

5 ml flip top vial

SAMPL ES
requested

ABELING
satisfactory per K. Johnson

IOLOGIC AVAILABILITY
NA

STABILIZATION INSPECTION
requested

PONENTS, COMPOSITION, MANUFACTURING, CONTROLS
see issued letter

ACKAGING
1 ml, type 1 — amber ampul

STABILITY
Protocol: satisfactory

Exp. Date: 12 mo w/challenge data

REMAINDER
1. [ ]
CONCLUSION: 2. [ ]
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<th>COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS</th>
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| STABILITY: Protocol:                        | satisfactory                 |
| Exp. Date:                                  | 12 mo w/challenge data       |

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\[ \sum_{i=1}^{n} x_i = 16 - \delta^2 \]
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

87-955

ADMINISTRATIVE DOCUMENTS
MEMORANDUM

From: Division of Generic Drug Monographs, HFD-530

Requester's Name: David Rosen

Phone: 443-4040

Subject: GMP Evaluation Request

NoA, ANDA, and Supplement Number: 87-954 (2 mg/ml 0.5 ml ampul) 87-955 (10 mg/ml 1 ml vial) 87-956 (10 mg/ml 5 ml Flip-top vial)

Drug Trade Name: Vitamin K1

Drug Non-Proprietary Name: Phytonadione Injection

Drug Classification: A or B

IC

Other

Product Code: SVP

(Description of dosage form, e.g., compressed tablet; coated tablet; soft gelatin capsule; liquid; See Table)

180 Day Date: 11-11-82

Applicant's Name: Abbott Laboratories

Address: Abbott Park, North Chicago, IL 60064

Facilities to be Evaluated: (Name, Address, and Responsibility)

2. Abbott Labs., Rocky Mount, NC 27801  Manual Finished Dosage Form

3. Hoffman-LaRoche Inc., Nutley, NJ 07110  193026

FOR HFD-320 USE ONLY

Date Received: Date Completed:

cc: HFD-320 (Orig)

HFD-530 (2 Copies)
[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 Kinseland Avenue, Nutley, N.J. 07110 (NDA 2-718).
   b. Menadiol sodium diphosphate; marketed as Synkayvite Tablets by Roche Laboratories, Division of Hoffman-LaRoche, Inc. (NDA 3-718).

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


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.

1. 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:

a. Menadione sodium diphosphate and menadione sodium bisulfite injection are effective for the indications stated in the labeling conditions in paragraph IC.

b. Although menadion sodium diphosphate and menadione sodium bisulfite injection are effective in preventing hemorrhagic disease of the newborn, the risks associated with the use of these drugs in the newborn 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 that menadione sodium diphosphate and menadione sodium bisulfite injection are effective for the following indications for which one or both drugs are recommended: prophylaxis, to prevent 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:

Indications

Vitamin K deficiency secondary to the administration of antibiotics and other and to prevent and/or treat the administration of vitamin K deficiency.

Hypoprothrombinemia secondary to obstruction of jaundice and biliary fistulae. Bile salts may be administered concurrently.

Menadione is ineffective alone. The menadione salts may be effective alone.

Hypoprothrombinemia secondary to administration of salicylates.

II. Menadion 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:

a. Menadion sodium diphosphate and menadione sodium bisulfite injection are effective for the indications stated in the labeling conditions in paragraph IC.

These drugs are also effective for use as a liver function test. This use does not appear in the indications in paragraph C, as such use is now probably g and, however, it may be included in the labeling with properly qualifying comments.

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:

Indications

Anticoagulant-induced prothrombin deficiency.

Hypoprothrombinemia secondary to antibacterial therapy.

Hypoprothrombinemia secondary to administration of salicylates.

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

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

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

2. Phynadione 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 obstetric use; low prothrombin values incident to other prothrombin-depressing drugs; severe liver disease; and prevention of excessive bleeding due to hypoprothrombinemia in surgical procedures, amputation, hysterectomy, 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:

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

Other drug-induced hypoprothrombinemia where it is definitely shown that the reaction is unrelated 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. 1, 1962) for such drug submitted within 180 days of the date of this publication to the Food and Drug Administration may be provided with the labeling conditions described herein.

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, the applicant 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 information 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.

VII. Exemption from official periodic reporting. The 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), (3), and (5) also are waived in respect to the 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 (c) 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 included in the application as published in the Federal Register April 24, 1970 (35 F.R. 6574).

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 (a) and (d) 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. 30 days for updating information.

3. Marketing of the drug may continue until the supplemental applications submitted in accord with the preceding subparagraphs (a) and (c) 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.

4. In accordance with the provisions of section 508 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, the right to be heard by such an order, an opportunity for a hearing to show why such applications 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.

5. Data from well-controlled clinical investigations (identified for ready review) as described in § 130.12 (a) of the regulations published in the Federal Register of May 8, 1970 (35 F.R. 7230). 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.

6. Unapproved use or form of drug.

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 unless good scientific evidence is filed with the Commissioner before the end of the 60 days following the date of publication of this notice that such use is approved in a new-drug application or is otherwise in accord with this announcement.

A copy of the NWC-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 DESR 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. 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 NWC-NRC reports: Press Relations Office (CE-200), Food and Drug Administration, 5600 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.

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

FEDERAL REGISTER, VOL. 35, NO. 165—TUESDAY, AUGUST 25, 1970
REVIEW OF PROFESSIONAL LABELING

ANDA - FPL

ANDA #: 87-954
     87-955
     87-956

CO. NAME: Abbott

NAME OF DRUG: Trade: Vitamin K1
               Generic: Phytonadione Injection

DATE OF SUBMISSION: April 30, 1982

COMMENTS:

Container:

   a) Should also note IV, as a route of administration.
   b) The expression of strength should be more prominent 10 mg
      or 1 mg

      The 1 mg ampul (2 mg/ml, 0.5 ml) is especially poor.

Carton: same as above

Package Insert:

   HOW SUPPLIED section

   Column 2

   9157      --0.5-ml--     1
   9158      --1.0-ml--     10...
   9160      --5.0-ml--    50 mg

RECOMMENDATIONS:

1. Note above comments

2. [ ]

3. [ ]

4. Firm should incorporate above suggestions, and prepare and submit FPL of
   container, carton and package insert.

cc: K. T. Johnson

dup
KTJ/cj1/8-11-82
MEMORANDUM

TO:  Check appropriate box.

☐ Field Science Branch (HFO-130)
☐ Division of Drug Chemistry (HFO-420)
☐ ___________________ District Lab (HFR—)

DATE TO FSB: 3-9-83
DATE TO LABS: 
OPERATION CODE
PMS Code PAC 5-2832
HIA/DCC: BD—

FROM: Chang
NDE Chemist, (301) 443— (HFD—)

SUBJECT: Method Validation for NOA 87-954, 955, 956
Product: Vitamin K_1 Injection
Applicant: Abbott Labs, N. Chicago 60064
AF No. _______

We request verification by your laboratory of the proposed manufacturing controls (specifications and/or laboratory methodology) as described in the subject application. All information relative to this application should be held confidential in accordance with 21 CFR 314.14.

Please perform the indicated tests on the samples herewith forwarded and identified on the attached Methods Validation Request and Reporting Sheet, Form FD 2871a, and summarize your laboratory findings in item 4.

ESTIMATED ANALYTICAL TIME REQUIRED: _______ HRS. (Determined by HFO-130)

Because of the statutory time limits for processing applications, your report should be submitted promptly upon completion, but not later than _______.

Please contact NDE Chemist if requested completion date cannot be met.

<table>
<thead>
<tr>
<th>DISTRIBUTION AS INDICATED ON RIGHT:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Original Form FD 2871a and District Laboratory FD 2871a with attachments to Originating Chemist. Also include a statement of your conclusions as to suitability of proposed tests for control and regulatory purposes.</td>
</tr>
<tr>
<td>• One copy of your FD 2871a and statement to HFO-130.</td>
</tr>
<tr>
<td>• One copy of your FD 2871a to the District Laboratory which also ran a validation test.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DESIGNATED DISTRICT LABORATORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Original of Form FD 2871a with attachments (original analytical worksheets, any spectra, graphs, curves, calculations and accompanying memos) to DDC (HFO-420)</td>
</tr>
<tr>
<td>• One copy of FD 2871a to NDE contact Chemist.</td>
</tr>
<tr>
<td>• One copy of FD 2871a to FSB (HFO-130)</td>
</tr>
</tbody>
</table>

SAMPLE ACCOUNTABILITY (Completed by NDE Drug Sample Custodian)

<table>
<thead>
<tr>
<th>RECEIVED:</th>
<th>DATE</th>
<th>INITIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDE Sample Room</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FORWARD TO:</th>
<th>DATE</th>
<th>INITIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>District Lab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDC (HFO-420)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RETURN THIS COPY TO:
(checked box)

☐ Originating Chemist  C. Chang (HFD—530)

ENCLOSURES: Form FD 2871a and proposed manufacturing controls.

FORM FD 2871 (10/75)
## METHODS VALIDATION REQUEST AND REPORTING RECORD

### SAMPLES BEING FORWARDED

<table>
<thead>
<tr>
<th>ITEM</th>
<th>QUANTITY</th>
<th>CONTROL NO. OR OTHER IDENTIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K&lt;sub&gt;1&lt;/sub&gt; Injection 10 mg/ml (37-956)</td>
<td>x 5 ml vials</td>
<td>#I-10-A</td>
</tr>
</tbody>
</table>

### Photocopies of these items are attached:

<table>
<thead>
<tr>
<th>Statement of Composition of Finished Dosage Form(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specifications/Methods for New Drug Substance(s)</td>
</tr>
<tr>
<td>Specifications/Methods for Finished Dosage Form(s)</td>
</tr>
<tr>
<td>Results of Determinations obtained by Applicant(s)</td>
</tr>
<tr>
<td>Other: (Specify)</td>
</tr>
</tbody>
</table>

### REQUESTED DETERMINATIONS (Perform tests indicated below; conduct ASSAY tests in DUPLICATE.)

- Drug Substance(s):
- Dosage Form(s):
  - Vitamin K<sub>1</sub>
  - Benzyl Alcohol

### SUMMARY OF RESULTS (Report individual and average ASSAY results)

- Ph Identifications
- As needed - make comments and recommendations on the suitability of the methods.

### SIGNATURE OF ANALYST          DATE

### DISTRICT LABORATORY COPY ROUTING | DIVISION OF DRUG CHEMISTRY COPY ROUTING

<table>
<thead>
<tr>
<th>Division of Drug Chemistry (HFD-420)</th>
<th>C Chang Chemist (HFD-530)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>District Laboratory (HFD-</td>
</tr>
<tr>
<td>Field Sciences Branch (HFD-130)</td>
<td>Field Sciences Branch (HFD-130)</td>
</tr>
</tbody>
</table>

FORM FD 2871 (10/73) For comments, use additional 8 x 10% sheets.
REVIEW OF PROFESSIONAL LABELING

Orig. Amendment - FPL

DATE OF REVIEW: 1-13-83
NAME OF FIRM: Abbott

ANDA #: 87-954
87-955
87-956

NAME OF DRUG: Trade: Vitamin K Injection
Generic: Phytonadione Injection

DATE OF SUBMISSION: December 27, 1982

COMMENTS:

Container: satisfactory
Carton: satisfactory
Insert: satisfactory

RECOMMENDATIONS:

1. Both container labels and insert labeling is satisfactory.

2. However, the firm should continue to explore a way to better express the total amount contained in the 1 mg ampul (perhaps an underline or a box).

3. The firm should also describe the presence of FDA on each label, and confirm such code will not go onto a commercial package.

cc: dup
KTJ/1/114-83

[Signature]

Kent J. Johnson
NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

TO: Press Relations Staff (HF1-40)
FROM: Bureau of Drugs

ATTENTION
Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION
[ ] ORIGINAL NDA [ ] SUPPLEMENT [ ] ABBREVIATED [ ] SUPPLEMENT
[ ] ORIGINAL NDA [ ] TO ANDA [ ] ABBREVIATED [ ] TO ANDA

CATEGORY
[ ] HUMAN [ ] VETERINARY

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG.

Vitamin K, (phytonadione)

DOSAGE FORM
Injection

HOW DISPENSED
[ ] RX [ ] OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)

Vitamin K \(_{1}\) (phytonadione) 10 mg/ml

NAME OF APPLICANT (Include City and State)
Abbott Laboratories
North Chicago, IL 60064

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY
Prothrombogenic vitamin

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY
NAME
C. Chang
DATE
7-19-83

FORM APPROVED BY
NAME
J. L. Meyer
DATE

FORM FD 1642 (2/73) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.
### Quantitative Composition of the Solution

<table>
<thead>
<tr>
<th>Scale per ml</th>
<th>Drug</th>
<th>Per Typical Batch</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0mg</td>
<td>Phytonadione, USP (Vitamin K₁ for Parenteral Use)</td>
<td></td>
</tr>
<tr>
<td>70.0mg</td>
<td>(Polyoxethylated fatty acid derivative)</td>
<td></td>
</tr>
<tr>
<td>37.5mg</td>
<td>Dextrose, Dextrose,</td>
<td></td>
</tr>
<tr>
<td>9.0mg</td>
<td>Alcohol, Benzyl, NF</td>
<td></td>
</tr>
<tr>
<td>q.s.</td>
<td>Acid, Hydrochloric,</td>
<td>q.s.</td>
</tr>
<tr>
<td>q.s.</td>
<td></td>
<td>q.s.</td>
</tr>
<tr>
<td>q.s.</td>
<td>Water for Injection, USP</td>
<td></td>
</tr>
</tbody>
</table>

* for pH adjustment
Abbott Laboratories
Attention: Mr. Frederic A. Gustafson
Abbott Park
North Chicago, IL 60064

Gentlemen:

Please refer to your new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vitamin K₁ (phytonadione) Injection, U.S.P., 10 mg/ml, in 1 ml Ampul.

Reference is also made to your communications dated March 8, April 15, and May 16, 1983.

The application is deficient and therefore not approvable under Section 505(b) of the Act as follows:

Our laboratory has made the following comments with respect to your sample and methodology:

(1)
The file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.110(d). If you do so, the application shall be re-evaluated and within 90 days of the date of receipt of such request (or additional period as we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours,

[Signature]

Martin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of the Associate Director for Drug Monographs
Office of Drugs
National Center for Drugs & Biologics

cc:
CHI-DO
HFN-530
JLMeyer/CChang
R/DinitJMeyer/MSeife
ft/cjl/7-8-83
not approvable
July 8, 1983

NATIONAL CENTER FOR DRUGS AND BIOLOGICS, HFN #530
Attn: DOCUMENT CONTROL ROOM #16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Marvin Seife, M.D.
Director

RE: Vitamin K<sub>1</sub> Injection (Phytonadione Inj., USP), NDA 87-954
Vitamin K<sub>1</sub> Injection (Phytonadione Inj., USP), NDA 87-956

Gentlemen:

Reference is made to a telephone conversation between Mr. Charles Chang of the Administration and Mr. James E. Murray of Abbott Laboratories on July 8, 1983. Based on that conversation, we understand that minor differences exist between the analytical justification supplied in the new drug applications and the results of the method validation.

We hereby commit to resolve these issues as soon as possible and request that the Administration approve the applications as provided for in Mr. Halperin’s memo concerning method validation.

Sincerely,

Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division

JEM/ts
0523f/119

RECEIVED
JUL 13 1983
GENERIC DRUGS
May 16, 1983

NATIONAL CENTER FOR DRUGS AND BIOLOGICS, HFN #530
Attn: DOCUMENT CONTROL ROOM #16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Marvin Seife, M.D.
Director

RE: Vitamin K1 (Phytonadione Injection, USP)
NDA 87-954, 87-955, 87-956

Gentlemen:

In response to a request from Mr. Charles Chang of the Administration, the following sample is being sent to Mr. Dick Thompson of the Minneapolis District Laboratory:

This is sufficient material to run more than three replicates of the final product assay for_____

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson
Director
Regulatory Affairs
Hospital Products Division
(312) 937-3213

cc: Mr. Dick Thompson
FDA District Laboratory
240 Hennepin Ave.
Minneapolis, Minnesota 55401
(612) 725-2128

RECEIVED
MAY 19 1983
GENERIC DRUGS
April 15, 1983

NATIONAL CENTER FOR DRUGS AND BIOLOGICS, HFD #530
Attn: DOCUMENT CONTROL ROOM #16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Marvin Seife, M.D.
Director

RE: Vitamin K₁ Inj. (Phytonadione Inj., USP), 10mg/ml, 1ml ampul,
NDA 87-955
Vitamin K₁ Inj. (Phytonadione Inj., USP), 2mg/ml, 0.5ml ampul,
NDA 87-954
Vitamin K₁ Inj. (Phytonadione Inj., USP), 5ml Flip Top Vial,
NDA 87-956

Gentlemen:

Reference is made to the Administration's letters dated March 21, 1983 concerning the subject new drug applications. The following represents our response to the Administration's comments:

Comment 1: "It fails to include the appropriate DMF from both
previously requested."

Response: The manufacturing controls data was submitted January 11, 1983 by a__ A letter of authorization was provided in our February 4, 1983 amendment.

The ____________ submitted their manufacturing controls data for phytonadione on March 8, 1983. Appended as Exhibit I is a letter of authorization from the

Comment 2: "It fails to include the certificate of analysis from
____ It is recommended that in addition to ____ the complete U.S.P. monograph test be
performed by

RECEIVED
APR 15 1983

GENERIC DRUGS
Response: A certificate of analysis from [manufacturer] was supplied in our December 27, 1982 submission. Appended as Exhibit II is a letter from [manufacturer] stating that "tests the phytonadione followed by USP tests per the USP specifications.

A certificate of analysis detailing the results of the USP tests is also appended. In addition, the material is tested against USPXX specifications upon receipt by Abbott Laboratories as defined in the raw material specification for Phytonadione, USP, Drug Code 56984, p. 49 of the original submission.

We trust that our submissions are now complete and request an expeditious approval.

Sincerely,

ABBOTT LABORATORIES

[Signature]

Frederick A. Gustafson
Director
Regulatory Affairs
Hospital Products Division

JEM/ts
Attachments
0685f/6
Exhibit I
Redacted 2

pages of

trade secret and/or

confidential

commercial

information
Exhibit II
Redacted

pages of

trade secret and/or

confidential

commercial

information
Abbott Laboratories  
Attention: Mr. Frederic A. Gustafson  
Abbott Park  
North Chicago, IL  60064  

Gentlemen:

Please refer to your new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vitamin K1 (phytonadione) Injection, U.S.P., 10 mg/ml in 1 ml Ampuls.

Reference is also made to your communications dated December 27, 1982, January 31, and February 4, 1983.

The application is deficient and therefore not approvable under Section 505(b) of the Act as follows:

(1) It fails to include the appropriate DMF from both and as previously requested.

(2) It fails to include the certificate of analysis from . It is recommended that in addition to the complete U.S.P. monograph tests be performed by

The file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.110(d). If you do so, the application shall be re-evaluated and within 30 days of the date of receipt of such request (or additional period as we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours,

[Signature]

[Name]

Director

Division of Generic Drug Monographs

Office of the Associate Director for Drug Monographs

Office of Drugs

National Center for Drugs and Biologics
February 4, 1983

NATIONAL CENTER FOR DRUGS AND BIOLOGICS, HFD #530
Attn: DOCUMENT CONTROL ROOM #16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Marvin Seife, M.D.
Director

RE: Vitamin K₁ Injection (Phytonadione Inj., USP), 10mg/ml, 1ml ampul,
NDA 87-955
Vitamin K₁ Injection (Phytonadione Inj., USP), 2mg/ml, 0.5ml ampul,
NDA 87-954
Vitamin K₁ Injection (Phytonadione Inj., USP), 5ml Flip-top Vial,
NDA 87-956

Gentlemen:

Abbott Laboratories hereby amends our supplemental applications dated December 27, 1982 which were submitted in response to the Administration's letter dated August 23, 1982. The purpose of this amendment is to provide a letter of authorization from allowing the Administration to access the data supplied by them January 11, 1983 when reviewing our pending NDA's for Vitamin K₁ Injection. is a of the active ingredient of the subject NDA's, namely Phytonadione USP. Appended is a copy of the letter of authorization.

Sincerely,

Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division

JEM / ts
Attachment
0600f
Redacted 4

pages of

trade secret and/or

confidential

commercial

information
December 27, 1982

NATIONAL CENTER FOR DRUGS AND BIOLOGICS, HFD #530
Attn: DOCUMENT CONTROL ROOM #16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Marvin Seife, M.D.
Director

RE: Vitamin K1 Inj. (Phytonadione Inj., USP), 10mg/ml, 1ml ampul,
    NDA 87-955
    Vitamin K1 Inj. (Phytonadione Inj., USP), 2mg/ml, 0.5ml ampul,
    NDA 87-954
    Vitamin K1 Inj. (Phytonadione Inj., USP), 10mg/ml, 5ml Fliptop Vial,
    NDA 87-956

Gentlemen:

Reference is made to the Administration's letter dated August 23, 1982
concerning our submissions dated April 30, 1982 for Vitamin K1 Injection.
The letter requested additional manufacturing controls information and a
labeling change. The following represents our response:

Comment 1: "It fails to submit the correct labeling
    information. In this regard:

   a. Container and Carton labels:

   b.
c. Package insert

<table>
<thead>
<tr>
<th>How Supplied Section</th>
<th>Column 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>9157</td>
<td>1mg (0.5 ml)</td>
</tr>
<tr>
<td>9158</td>
<td>10 mg (1 ml)</td>
</tr>
<tr>
<td>9160</td>
<td>50 mg (5 ml).</td>
</tr>
</tbody>
</table>

Response:

The container labels, cartons, and "How Supplied" section of the package enclosure have been revised to increase the prominence of the total dosage as well as the fill volume and concentration/ml of Vitamin K₁. In addition, the package enclosure has been revised to comply with the Administration's Labeling Guidelines (Revised 9/82) for Phytonadione Injection.

Appended as Exhibit I are twelve (12) copies of the revised final printed labeling.
Redacted

2

pages of

trade secret and/or

confidential

commercial

information
We trust that this adequately answers the Administration's comments and request an expeditious approval.

Sincerely,

ABBOTT LABORATORIES

Frederick A. Gustafson
Director
Regulatory Affairs
Hospital Products Division

JEM/ts
Attachments
0526f
December 7, 1982

NATIONAL CENTER FOR DRUGS AND BIOLOGICS, HFD #530
Attn: DOCUMENT CONTROL ROOM #16-72
5600 Fishers Lane
Rockville, Maryland  20857

ATTENTION: Marvin Seife, M.D.
Director

RE: Vitamin K₁ Injection (Phytonadione Injection, USP), NDA 87-954
    Vitamin K₁ Injection (Phytonadione Injection, USP), NDA 87-955
    Vitamin K₁ Injection (Phytonadione Injection, USP), NDA 87-956

Gentlemen:

Reference is made to the Administration's letters dated August 23, 1982 which requested samples and analytical results of the finished dosage form.

Appended are the analytical results for Vitamin K₁ Injection, 10mg/ml in 5ml Vials, Lot I-10-A. Samples of the subject finished dosage form are being hand delivered to the Administration. The samples consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the subject applications. The samples are being submitted in support of the three subject new drug applications.

Sincerely,

Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division

JEM/ts
Attachments
0504f
Abbott Laboratories
Attention: Mr. Frederic A. Gustafson
Abbott Park
North Chicago, IL  60064

Gentlemen:

Please refer to your abbreviated new drug application dated April 30, 1982, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Vitamin K, (Phytonadione) Injection U.S.P., 10 mg/ml, 1 ml ampul.

The application is deficient and therefore not approvable under Section 505(b) of the Act as follows:

1. It fails to submit the correct labeling information. In this regard:

   c. Package insert

   How Supplied Section  
   Column 2
   9157  1 mg (0.5 ml)
   9158  10 mg (1 ml)
   9160  50 mg (5 ml)

3. It fails to include the manufacturer's Certificate of Analysis and their appropriate DMF from both

4. It fails to submit a commitment to perform all of the procedures listed therein.
5. It fails to submit samples and analytical results of the finished dosage form for the lot submitted.

6. It fails to submit adequate stability studies. In this regard:

The file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.110(d). If you do so, the application shall be re-evaluated and within 90 days of the date of receipt of such request (or additional period as we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours,

\[signature\]

8/23/82

\[date\]

\[name\], M.D.

Director

Division of Generic Drug Monographs

Office of the Associate Director

for Drug Monographs

Office of Drugs

National Center for Drugs and Biologics

cc: CHI-DO

HFD-614

HFD-530

RD: KJohnson/JLMeyer/CChang

RD Init: JMeyer/MSeife

MSeife 8/10/82

ft/vmp/8/16/82 (2655 pl7)

not approvable
Abbott Laboratories
Attention: Frederick A. Gustafson
Abbott Park
North Chicago, IL 60064

Gentlemen:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME OF DRUG: Vitamin K₁ Injection (Phytonadione Injection; USP)
10 mg/ml, 1 ml ampul

DATE OF APPLICATION: April 30, 1982
DATE OF COVER LETTER: April 30, 1982
DATE OF RECEIPT: May 11, 1982

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the NDA number shown above.

[Signature]

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of Drug Monographs
Bureau of Drugs and Biologics

CHI-DO DUR HFD-530
JLMeier 1-4-82 9-0-07
ack
April 30, 1982

BUREAU OF DRUGS, HFD #530
Attn: DOCUMENT CONTROL ROOM # 16-72
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: Marvin Seife, M.D.
Director

RE: Vitamin K₁ Injection (Phytonadione Injection, USP)
ORIGINAL ABBREVIATED NEW DRUG APPLICATION

Gentlemen:

Abbott Laboratories hereby submits an original abbreviated new drug application for the above referenced drug in accordance with the Federal Register DESI Notice 2139 of August 25, 1970. The drug is essentially identical in formulation to the currently available Phytonadione Injection marketed as Aqua MEPHYTON Injection by Merck, Sharp & Dohme.

The drug will be supplied as a sterile, nonpyrogenic aqueous dispersion in the following dosage form:

List 9158 Vitamin K₁ Injection (Phytonadione Inj. USP), 10mg/ml, 1ml ampul

Please refer to the accompanying table of contents for the data supporting this submission. We trust that this submission is complete in all respects and would appreciate an expeditious review.

Sincerely,

[Signature]

Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division

JEM: jkf
Attachments
0454n