CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

87-955

Generic Name: Vitamin K_1

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

NDA 87-955

JUL 25 1983

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 314.8 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 asure 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 not 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.

Sincerely yours,

/S/ 7/25/83

Marvin 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

/S/ 7-20-83

/S/ 7/20/83

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

87-955

Final Printed Labeling

Exhibit I

Final Printed Labeling

ORIGINAL

Labeling: JAN 3 1983

NDA No: 87955 Rec'd.

Reviewed by: /S/ 7-26-83

NDC 0074-9158-01

1 ml

Vitamin K_1 Inj.
PHYTONADIONE
INJ., USP
10 mg (10 mg/ml)
Protect from light.
FDA1177 10/82
Abbott Laboratories
No. Chicago, IL60064

APPROVED
JUL 25 1983

APPROVED

JUL 25 1983

Vitamin K_1 Inj.

PHYTONADIONE INJECTION, USP

10 mg (10 mg/ml)

Protect from light.

1 ml Single-dose Ampul 25 Units NDC 0074-9158-01

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

Each ml contains phytonadione 10 mg; polyoxyethylated fatty acid derivative 70 mg; dextrose, hydrous 37.5 mg; benzyl alcohol 9 mg added as preservative. May contain hydrochloric acid for pH adjustment.

Approx. pH 6

Sterile, nonpyrogenic.

Exp.

Lot

FDA1178-10/82 Printed in USA

Vitamin K_1 Injection

PHYTONADIONE INJ., USP

Aqueous Colloidal Solution of Vitamin K_1

Ampul

Fliptop Vial

WARNING – INTRAVENOUS USE

Severe reactions, including fatalities, have occurred during and immediately after INTRAVENOUS injection of phytonadione 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 and cardiac and/or respiratory arrest. Some patients have exhibited these severe reactions on receiving phytonadione 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.

APPROVED
JUL 25 1983

Protect from light.

Do not freeze or expose to extreme heat.

Caution: Federal (USA) law prohibits dispensing without prescription.

Abbott FDA1218-Rev. Nov. 1982 Printed in USA

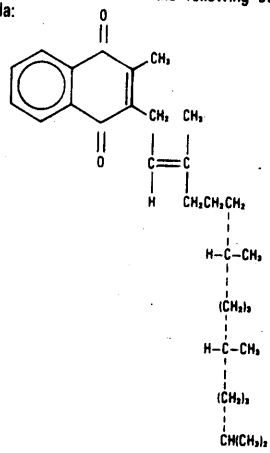
ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

DESCRIPTION

Vitamin K_1 Injection (Phytonadione Injection, USP) is a yellow, sterile, nonpyrogenic aqueous colloidal solution available for injection by the intravenous, intramuscular and subcutaneous routes. Each milliliter contains phytonadione 2 or 10 mg, polyoxyethylated 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.

Phytonadione, USP is chemically designated 2-methyl-3-(3,7,11,15-tetramethyl-2-hexadecenyl)-1,4-Naphthalenedione, ($C_{31}H_{46}O_2$), a viscous liquid,

insoluble in water. It has the following structural formula:



CLINICAL PHARMACOLOGY

Vitamin K_1 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 X). 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_1 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_1 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, biliary 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.

Benzyl alcohol 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 benzyl 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 conteract 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_1 Injection (Phytonadione Injection, USP) is used to correct excessive anticoagulant-induced hypoprothrombinemia, anticoagulant therapy still being indicated, 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_1 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_1 Injection. It is also not known whether Vitamin K_1 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Vitamin K_1 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 prematures when receiving doses above those recommended. This effect, with its possibility of attendant kernicterus, should be borne to 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.

DOSAGE AND ADMINISTRATION

Whenever possible, Vitamin K_1 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 refractoriness 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_1 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_1 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_1 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/liter.

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.

HOW SUPPLIED

Vitamin K_1 Injection (Phytonadione Injection, USP) is supplied as follows:

List No.	Container	Amount of Vitamin K_1 Inj. in Container	Concentration of Vitamin K_1 Inj.
9157	1 ml Ampul	1 mg	(0.5 ml) 2 mg/ml
9158	1 ml Ampul	10 mg	(1.0 ml) 10 mg/ml
9160	5 ml Fliptop Vial	50 mg	(5.0 ml) 10 mg/ml

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

87-955

CHEMISTRY REVIEW(S)

CHEMIST's REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Statement Date: DESI 2139

NDA NUMBER: 87-955

NAME AND ADDRESS OF APPLICANT

Abbott Labs. - N. Chicago 60064

ORIGINAL
AMENDMENT
SUPPLEMENT XX
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

control & lab results

DATE(s) of SUBMISSION

as per letter

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
Prothrombogenic vitamin	Phytonadione (Vitamin K1)	RX XX OTC ___
DOSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/DMF
injection (aqueous colloidal	10 mg/ml	87-955 10 mg/ml 1 ml am 87-954 2mg/ml 0.5 ml a 87-956 10 mg/ml
STERILIZATION	SAMPLES	5 ml flip top vi
	requested	

LABELING

satisfactory per KJohnson

BIOLOGIC AVAILABILITY

NA

ESTABLISHMENT INSPECTION

Not rec'd at init

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

~~see~~ Satisfactory

PACKAGING

1 ml, type 1 ——, amber ampul

STABILITY

Protocol: satisfactory

Exp. Date: 12 mo w/challenge data

REMARKS AND CONCLUSION: 1

2

1

CChang — not approvable

/S/ 7-20-83

CHEMIST's REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT	Statement Date. DESI 2139	NDA NUMBER: 87-955

NAME AND ADDRESS OF APPLICANT
Abbott Labs. - N. Chicago 60064

ORIGINAL
AMENDMENT
SUPPLEMENT **XX**
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT
control & lab results

DATE(s) of SUBMISSION
as per letter

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
Prothrombogenic vitamin	**Phytonadione (Vitamin K1)**	RX **XX** OTC ____

DOSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/DMF
injection (aqueous colloidal	**10 mg/ml**	**87-955 10 mg/ml 1 ml ampul** **87-954 2mg/ml 0.5 ml ampi** **87-956 10 mg/ml 5 ml flip top vial**

STERILIZATION	SAMPLES
	requested

LABELING **satisfactory per KJohnson**

BIOLOGIC AVAILABILITY
NA

ESTABLISHMENT INSPECTION
requested

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
see issued letter

PACKAGING
1 ml, type 1 ——— amber ampul

STABILITY
Protocol: **satisfactory**

Exp. Date: **12 mo w/challenge data**

REMARKS AND CONCLUSION:
1.
2.

/S/ 7-11-85

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT	Statement Date: DESI 2139	NDA # 87-955

NAME AND ADDRESS OF APPLICANT:

Abbott Labs - N. Chicago, IL 60064

ORIGINAL
AMENDMENT
SUPPLEMENT
RESUBMISSION XX
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

labeling and control information

DATE(s) of SUBMISSION(s)

as per letter

PHARMACOLOGICAL CATEGORY	NAME OF DRUG
Prothrombogenic vitamin	Phytonadione (Vitamin K_1)

HOW DISPENSED

RX XX OTC ____

DOSAGE FORM	POTENCY(IES)
injection (aqueous collodial solution)	10 mg/ml
STERILIZATION	SAMPLES
	Requested

RELATED IND/NDA/DMF

87-955 10 mg/ml 1 ml amp
87-954 2 mg/ml 0.5 ml am
87-956 10 mg/ml
5 ml flip top via

LABELING

satisfactory per KJohnson

BIOLOGIC AVAILABILITY

NA

ESTABLISHMENT INSPECTION

requested

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

see issued letter

PACKAGING

1 ml, type 1 ——— amber ampul

STABILITY:

Protocol: satisfactory

Exp. Date: 12 mo w/challenge data

REMARKS & CONCLUSION:

Note: 1) p

2)

CChang Not approvable

/S/ 3-18-83

ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT | DESI 2139 | 87-955

NAME AND ADDRESS OF APPLICANT:

Abbott Labs - N. Chicago, IL 60064

ORIGINAL XX
AMENDMENT
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

DATE(s) of SUBMISSION(s)

as per letter

PHARMACOLOGICAL CATEGORY	NAME OF DRUG
Prothrombogenic vitamin K	phytonadione (Vitamin K_1)
DOSAGE FORM	POTENCY(IES)
injection (aqueous colloidal solution)	10 mg/ml
STERILIZATION	SAMPLES
———	Requested

HOW DISPENSED

RX XX OTC ———

RELATED IND/NDA/DMF

87-955 10 mg/ml 1 mlam
87-954 2 mg/ml 0.5 ml ampul
87-956 10 mg/ml 5 ml flip top vi

LABELING

unsatisfactory per KJOhnson

BIOLOGIC AVAILABILITY

NA

ESTABLISHMENT INSPECTION

requested

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

See issued letter

PACKAGING

1 ml, type i ———, amber ampul

STABILITY:

Protocol: satisfactory

Exp. Date: 12 mo w/challenge data

REMARKS & CONCLUSION: Note: 1) [redacted]

2) [redacted]

CChang Not approvable

/S/ -16-82

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

87-955

ADMINISTRATIVE DOCUMENTS

MEMORANDUM

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Division of Drug Manufacturing, HFD-320 DATE: 5-13-82

FROM : Division of Generic Drug Monographs, HFD- 530

Requester's Name: David Rosen Phone: 443-4040

SUBJECT: GMP EVALUATION REQUEST

NDA, 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 Fliptop vial)

DRUG Trade Name: Vitamin K_1

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)

1. [redacted]

2. Abbott Labs., Rocky Mount, NC 27801 Manuf finished Dosage Form

3. [redacted]

4. [redacted]

FOR HFD-320 USE ONLY

Date Received: ___ Date Completed: ___

cc: HFD-320 (Orig)
HFD- (2 Copies)

[redacted] COMMENTS CONCERNING THIS REQUEST SHOULD BE DESCRIBED ON AN ATTACHED SHEET

[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 a[illegible]ic; however, it may be included in th[illegible]abeling 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.]

REVIEW OF PROFESSIONAL LABELING

ANDA - FPL

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

CO. NAME: Abbott

NAME OF DRUG: Trade: Vitamin K_1

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.

Kent T. Johnson

cc:
dup
KTJ/cjl/8-11-82

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : *Check appropriate box.*

- ☐ Field Science Branch (HFO-130)
- ☐ Division of Drug Chemistry (HFD-420)
- ☐ _____ District Lab (HFR-____)

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

FROM : CChang _____ NDE Chemist, (301) 443-____ (HFD-___)

SUBJECT: Method Validation for NDA 87-954, 955, 956
Product Vitamin K1 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.

DISTRIBUTION AS INDICATED ON RIGHT:	DIVISION OF DRUG CHEMISTRY	DESIGNATED DISTRICT LABORATORY
	• 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. • One copy of your FD 2871a and statement to HFO-130. • One copy of your FD 2871a to the District Laboratory which also ran a validation test.	• Original of Form FD 2871a with attachments *(original analytical worksheets, any spectra, graphs, curves, calculations and accompanying memos)* to DDC (HFD-420) • One copy of FD 2871a to NDE contact Chemist. • One copy of FD 2871a to FSB (HFO-130)

SAMPLE ACCOUNTABILITY *(Completed by NDE Drug Sample Custodian)*

		DATE	INITIALS
RECEIVED:	NDE Sample Room		
FORWARDED TO:	_____ District Lab		
	DDC (HFD-420)		

RETURN THIS COPY TO: (Check box)
☒ Originating Chemist C.Chang (HFD-N 530)

ENCLOSURES: Form FD 2871a and proposed manufacturing controls.

6p

FORM FD 2871 (10/75)

METHODS VALIDATION REQUEST AND REPORTING RECORD

NDA NO.

1. SAMPLES BEING FORWARDED

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION
Vitamin K_1 Injection 10 mg/ml (87-956)	x 5 ml vials	#I-10-A

2. Photocopies of these items are attached:

	No. of Pages	NDA Page Number(s)
Statement of Composition of Finished Dosage Form(s)		
Specifications/Methods for New Drug Substance(s)		
Specifications/Methods for Finished Dosage Form(s)		
Results of Determinations obtained by Applicant(s)		
Other: (Specify)		

3. REQUESTED DETERMINATIONS *(Perform tests indicated below: (conduct ASSAY tests in DUPLICATE.)*

a. Drug Substance(s):

b. Dosage Form(s):
Vitamin K_1
Benzyl Alcohol

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

4. SUMMARY OF RESULTS *(Report individual and average ASSAY results)*

SIGNATURE OF ANALYST

DATE

DISTRICT LABORATORY COPY ROUTING		DIVISION OF DRUG CHEMISTRY COPY ROUTING	
	Division of Drug Chemistry (HFD-420)		C Chang Chemist (HFD-530)
	_____ Chemist (HFD-____)		_____ District Laboratory (HFR-____)
	Field Sciences Branch (HFO-130)		Field Sciences Branch (HFO-130)

FORM FD 2871a (10/75) For comments, use additional 8 x 10½ 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.

Kent T. Johnson

cc:
dup
KTJ/cl/1[illegible]14-83

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 87-955

DATE APPROVAL LETTER ISSUED: JUL 25 1983

TO: Press Relations Staff (HFI-40)

FROM:
- [XX] Bureau of Drugs
- [ ] Bureau of Veterinary Medicine

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 TO NDA
- [XX] ABBREVIATED ORIGINAL NDA
- [ ] SUPPLEMENT TO ANDA

CATEGORY
- [XX] HUMAN
- [ ] VETERINARY

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

Vitamin K_1 (phytonadione)

DOSAGE FORM

Injection

ORIGINAL ABBREVIATED

HOW DISPENSED
- [XX] 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 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

Quantitative Composition of the Solution

Scale per ml	Drug	Per Typical Batch
10.0mg	Phytonadione, USP (Vitamin K_1 for Parenteral Use)	
70.0mg	(Polyoxethylated fatty acid derivative)	
37.5mg	Dextrose,	
	Dextrose,	
9.0mg	Alcohol, Benzyl, NF	
q.s.	Acid, Hydrochloric,	q.s.
q.s.		q.s.
q.s.	Water for Injection, USP	

* for pH adjustment

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

87-955

CORRESPONDENCE

JUL 12 1983

NDA 87-955

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 K_1 (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,

/S/ 7/12/83

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

/S/ 7-11-83

ABBOTT

Orig

Hospital Products Division

Abbott Laboratories
Abbott Park
North Chicago, Illinois 60064

July 8, 1983

ORIG NEW CORRES

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: [redacted]
Vitamin K_1 Injection (Phytonadione Inj., USP), NDA 87-954
Vitamin K_1 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

Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division

JEM/ts
0523f/119

RECEIVED
JUL 13 1983
GENERIC DRUGS

ABBOTT

Hello

Hospital Products Division
Abbott Laboratories
Abbott Park
North Chicago, Illinois 60064

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 K_1, ~~Injection~~ (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

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

JEM:jb

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

ABBOTT

Orig

Hospital Products Division
Abbott Laboratories
Abbott Park
North Chicago, Illinois 60064

April 15, 1983

RESUBMISSION
NDA ORIG AMENDMENT

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 K_1 Inj. (Phytonadione Inj., USP), 10mg/ml, 1ml ampul, NDA 87-955
Vitamin K_1 Inj. (Phytonadione Inj., USP), 2mg/ml, 0.5ml ampul, NDA 87-954
Vitamin K_1 Inj. (Phytonadione Inj., USP), 5ml Fliptop 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 [redacted] as previously requested."

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

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

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

RECEIVED
APR 15 1983

GENERIC DRUGS

Response: A certificate of analysis from [redacted] manufacturer) was supplied in our December 27, 1982 submission. Appended as Exhibit II is a letter from [redacted] manufacturer) stating that " [redacted] tests the phytonadione [redacted] 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

Frederick A. Gustafson

Frederick A. Gustafson
Director
Regulatory Affairs
Hospital Products Division

JEM/ts
Attachments
0685f/6

Exhibit I

3/8/03
Letter

Redacted 2

pages of

trade secret and/or

confidential

commercial

information

Exhibit II

3/8/83
3/28/83
4/6/83
Letters

Redacted 6

pages of

trade secret and/or

confidential

commercial

information

MAR 21 1983

NDA 87-955

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 [redacted], and [redacted] as previously requested.

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

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,

/S/ 3/21/83

Marvin 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

CHI-DO HFN-530
KJohnson/JLMeyer/CCh
R/DinitJMeyer/MSeif
ftcjl/3-14-83
not approvable

/S/ 3-14-83
/S/ 3/14/83

ABBOTT

Hospital Products Division

Abbott Laboratories
Abbott Park
North Chicago, Illinois 60064

February 4, 1983

ORIG NEW CORRES

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 K_1 Inj. (Phytonadione Inj., USP), 10mg/ml, 1ml ampul, NDA 87-955
Vitamin K_1 Inj. (Phytonadione Inj., USP), 2mg/ml, 0.5ml ampul, NDA 87-954
Vitamin K_1 Inj. (Phytonadione Inj., USP), 5ml Fliptop Vial, NDA 87-956

Gentlemen:

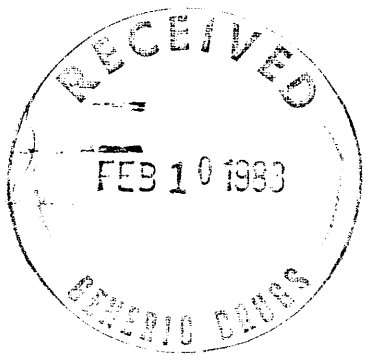
Abbott Laboratories hereby amends our supplemental applications dated December 27, 1982 which were submitted in response to the Administration's letter dated August 23, 1982. The purpose of this amendment is to provide a letter of authorization from [redacted] allowing the Administration to access the data supplied by them January 11, 1983 when reviewing our pending NDA's for Vitamin K_1 Injection. [redacted] is a [redacted] 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

Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division

JEM/ts
Attachment
0600f



1/31/83 & 1/11/83
Letters

Redacted 4

pages of

trade secret and/or

confidential

commercial

information

ABBOTT

Hospital Products Division

Abbott Laboratories
Abbott Park
North Chicago, Illinois 60064

Orig

December 27, 1982

RESUBMISSION

NDA ORIG AMENDMENT

FPL

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 K_1 Inj. (Phytonadione Inj., USP), 10mg/ml, 1ml ampul, NDA 87-955
Vitamin K_1 Inj. (Phytonadione Inj., USP), 2mg/ml, 0.5ml ampul, NDA 87-954
Vitamin K_1 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 K_1 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:

[redacted]

b. [redacted]

RECEIVED
JAN 3 1983
GENERIC DRUGS

c. Package insert

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

Response:

[redacted]

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 K_1. 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]

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

APPEARS THIS WAY
ON ORIGINAL

ABBOTT

file

Hospital Products Division

Abbott Laboratories
Abbott Park
North Chicago, Illinois 60064

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 K_1 Injection (Phytonadione Injection, USP), NDA 87-954
Vitamin K_1 Injection (Phytonadione Injection, USP), NDA 87-955
Vitamin K_1 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 K_1 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

Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division

JEM/ts
Attachments
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RECEIVED
DEC 10 1982
GENERIC DRUGS

NDA 87-955

AUG 23 1982

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 therin.

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,

/S/ 8/23/82

Marvin 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

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

/S/ 8-19-82

MAY 19 1982

NDA 87-955

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 K_1 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.

/S/ 5/19/82

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

CHI-DO DUR HFD-530
JLMeyer/ack 5-18-82
/S/ 5/18/82

ABBOTT

Hospital Products Division

Abbott Laboratories
Abbott Park
North Chicago, Illinois 60064

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 K_1 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 K_1 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,

Frederick A. Gustafson

Frederick A. Gustafson
Director, Regulatory Affairs
Hospital Products Division

JEM:jkf
Attachments
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