CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 17-651

Name: Heparin Sodium Injection USP

Sponsor: Lypho-Med, Inc.

Approval Date: February 10, 1978

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-651

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-651

APPROVAL LETTER

NDA 17-651

FEB 10 1978

Lypho-Med, Inc.
4020 West Division Street
Chicago, Illinois 60651

Gentlemen:

Reference is made to your new drug application dated September 18, 1974 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Heparin Sodium Injection, U.S.P. (derived from porcine intestinal mucosa).

We also acknowledge receipt of your additional communications and amendments dated September 28, 1976, February 23, 1977, August 3, 1977, and December 6, 1977 submitting final printed labeling.

In addition, we would appreciate your submitting in duplicate the advertising copy which you intend to use in your proposed promotional or advertising campaign. Please submit one of the copies directly to the Division of Drug Advertising with a copy of the package insert.

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

The enclosures summarize the conditions relating to the approval of this application.

Sincerely yours,

R.D.F.

Marion J. Finkel, M.D.
Associate Director for
New Drug Evaluation
Bureau of Drugs

Enclosures: Records and Reports Requirement (Reg 130.13)
Conditions of Approval of NDA

cc: CHI-DO
Orig. NDA
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JLangston/9/20/77
RWolters/9/20/77
RTemple/9/20/77
APPROVED

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RWolters 1-26-78
JLangston 2/2/78
AAGoering 1/26/78
JLangston 1/26/78
JVClavenard 2/1/78
AEAuer 1/23/78

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-651

APPROVED LABELING

All labeling enlarged to 130% by FOI staff.

HEPARIN SODIUM INJECTION, U.S.P.

DESCRIPTION: Heparin Sodium Injection, U.S.P. is a sterile solution of heparin sodium derived from animal tissues (porcine intestinal mucosa or beef lung, see label for organ and species), standardized for use as an anticoagulant, in water for injection. The potency is determined by biological assay using a U.S.P. reference standard based upon units of heparin activity per milligram.

ACTIONS: Heparin inhibits reactions which lead to the clotting of blood and the formation of fibrin clots both in vitro and in vivo. Heparin acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with antithrombin III (heparin co-factor) can prevent the development of a hypercoagulable state by inactivating activated Factor X, preventing the conversion of prothrombin to thrombin. Once a hypercoagulable state exists, larger amounts of heparin in combination with antithrombin III can inhibit the coagulation process by inactivating thrombin and earlier clotting intermediates, thus preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor.

Bleeding time is usually unaffected by heparin. Clotting time is prolonged by full therapeutic doses of heparin; in most cases it is not measurably affected by low doses of heparin.

Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

APPROVED

INDICATIONS: Heparin sodium injection is indicated for anticoagulant therapy in prophylaxis and treatment of venous thrombosis and its extension; in low-dose regimen for prevention of postoperative deep venous thrombosis and pulmonary embolism in patients undergoing major abdominothoracic surgery who are at risk of developing thromboembolic disease (see DOSAGE AND ADMINISTRATION section); for prophylaxis and treatment of pulmonary embolism; in atrial fibrillation with embolization; for diagnosis and treatment of acute and chronic consumptive coagulopathies (disseminated intravascular coagulation); for prevention of clotting in arterial and cardiac surgery; and for prevention of cerebral thrombosis in evolving stroke.

Heparin is indicated as an adjunct in treatment of coronary occlusion with acute myocardial infarction, and in prophylaxis and treatment of peripheral arterial embolism.

Heparin may also be employed as an anticoagulant in blood transfusions, extracorporeal circulation, dialysis procedures, and in blood samples for laboratory purposes.

CONTRAINDICATIONS: Hypersensitivity to heparin.

Inability to perform suitable blood coagulation tests, e.g. the whole blood clotting time, partial thromboplastin time, etc., at required intervals. There is usually no need to monitor the effect of low-dose heparin in patients with normal coagulation parameters.

Uncontrollable bleeding.

WARNINGS

Heparin sodium should be used with extreme caution in disease states in which there is an increased danger of hemorrhage.

Administration of Heparin Sodium Injection, U.S.P., when used in therapeutic dosage, should be regulated by frequent blood coagulation tests. If these are unduly prolonged or if hemorrhage occurs, heparin sodium should be promptly discontinued. See OVERDOSAGE section.

Some of the conditions in which increased danger of hemorrhage exists are:

Cardiovascular - subacute bacterial endocarditis; arterial sclerosis; increased capillary permeability; during and immediately following a) spinal tap or spinal anesthesia, b) major surgery, especially involving the brain, spinal cord, or eye.

Hematologic - conditions associated with increased bleeding tendencies such as hemophilia, some purpuras, and thrombocytopenia.

Gastrointestinal - inaccessible ulcerative lesions and continuous tube drainage of the stomach or small intestine.

ENLARGED TO 130% BY FDI STAFF

Heparin sodium may prolong the one-stage prothrombin time. Accordingly, when heparin sodium is given with dicumarol or warfarin sodium, a period of at least 5 hours after the last intravenous dose and 24 hours after the last subcutaneous (intrafat) dose of heparin sodium should elapse before blood is drawn, if a valid prothrombin time is to be obtained.

Drugs (such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole and hydroxochloroquine) which interfere with platelet aggregation reactions (the main hemostatic defense of heparinized patients) may induce bleeding and should be used with caution in patients on heparin therapy.

While there is experimental evidence that heparin may antagonize the action of ACTH, insulin, or corticoids, this effect has not been clearly defined.

There is also evidence in animal experiments that heparin may modify or inhibit allergic reactions. However, the application of these findings to human patients has not been fully defined.

Larger doses of heparin may be necessary in the febrile state.

The use of digitalis, tetracyclines, nicotine, or antihistamines may partially counteract the anticoagulant action of heparin. An increased resistance to heparin is frequently encountered in cases of thrombosis, thrombophlebitis, infections with thrombosing tendency, myocardial infarction, cancer, and in the postoperative patient.

USAGE IN PREGNANCY: Heparin sodium injection should be used with caution during pregnancy, especially during the last trimester and in the immediate post partum period.

There is no adequate information as to whether heparin may affect human fertility, or have a teratogenic potential or other adverse effects to the fetus.

Heparin does not cross the placental barrier; it is not excreted in human milk.

PRECAUTIONS: Because heparin sodium injection is derived from animal tissue, it should be used with caution in patients with a history of allergy. Before a therapeutic dose is given to such a patient, a trial dose of 1,000 units may be advisable.

Heparin sodium should also be used with caution in the presence of hepatic or renal disease, hypertension, during menstruation, or in patients with indwelling catheters.

A higher incidence of bleeding may be seen in women over 60 years of age.

Caution should be exercised when administering ACD-converted blood (i.e. blood collected in heparin sodium and later converted to ACD blood), since the anticoagulant activity of its heparin sodium content persists without loss for 22 days. ACD-converted blood may alter the coagulation system of the recipient, especially if it is given in multiple transfusions.

ADVERSE REACTIONS: Hemorrhage is the chief complication that may result from heparin therapy. An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug. See OVERDOSAGE section.

The occurrence of significant gastrointestinal or urinary tract bleeding during anticoagulant therapy may indicate the presence of an underlaying occult lesion.

Adrenal hemorrhage with resultant acute adrenal insufficiency has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patients who develop signs and symptoms compatible with acute adrenal hemorrhage and insufficiency. Plasma cortisol levels should be measured immediately, and vigorous therapy with intravenous corticosteroids should be instituted promptly. Initiation of therapy should not depend upon laboratory confirmation of the diagnosis, since any delay in an acute situation may result in the patient's death.

Intramuscular injection of heparin sodium frequently causes local irritation, mild pain, or hematoma, and for these reasons should be avoided. These effects are less often seen following deep subcutaneous (intrafat) injection. Histamine-like reactions have also been observed at the site of injection.

Hypersensitivity reactions have been reported with chills, fever, and urticaria as the most usual manifestations. Asthma, rhinitis, lacrimation, and anaphylactoid reactions have also been reported. Vasospastic reactions may develop independent of the origin of heparin, 6 to 10 days after the initiation of therapy and last for 4 to 6 hours. The affected limb is painful, ischemic and cyanosed. An artery to this limb may have been recently catheterized. After repeat injections, the reaction may gradually increase, to include generalized vasospasm, with cyanosis, tachypnea, feeling of oppression, and headache. Protamine sulfate treatment has no marked therapeutic effect. Itching and burning, especially on the plantar side of the feet, is possibly based on a similar allergic vasospastic reaction. Chest pain, elevated blood pressure, arthralgias, and/or headache have also been reported in the absence of definite peripheral vasospasm. Anaphylactic shock has been reported rarely following the intravenous administration of heparin sodium.

Acute reversible thrombocytopenia following the intravenous administration of heparin sodium has been reported. Osteoporosis, and suppression of renal function following long-term, high-dose administration, suppression of aldosterone synthesis, delayed transient alopecia, priapism, and rebound hyperlipemia following discontinuation of heparin sodium, have also been reported.

DOSAGE AND ADMINISTRATION: Heparin sodium is not effective by oral administration and should be given by deep subcutaneous (intrafat, i.e. above iliac crest or into the abdominal fat layer) injection, by intermittent intravenous injection, or intravenous infusion. The intramuscular route of administration should be avoided because of the frequent occurrence of hematoma at the injection site.

The dosage of heparin sodium should be adjusted according to the patient's coagulation test results, which during the first day of treatment should be determined just prior to each injection. There is usually no need to monitor the effect of low-dose heparin in patients with normal coagulation parameters. Dosage is considered adequate when the whole blood clotting time is elevated approximately 2.5 to 3 times the control value.

When heparin sodium is administered by continuous intravenous infusion, coagulation tests should be performed approximately every 4 hours during the early stages of therapy. When it is administered intermittently by intravenous, or deep subcutaneous (intrafat) injection, coagulation tests should be performed before each injection during the early stages of treatment, and daily thereafter.

When an oral anticoagulant of the coumadin, or similar type is administered with heparin sodium, coagulation tests and prothrombin activity should be determined at the start of therapy. For immediate anticoagulant effect, administer heparin sodium in the usual therapeutic dosage. When the results of the initial prothrombin determination are known, administer the first dose of an oral anticoagulant in the usual initial amount. Thereafter, perform a coagulation test and determine the prothrombin activity at appropriate intervals. A period of at least 5 hours after the last intravenous dose and 24 hours after the last subcutaneous (intrafat) dose of heparin sodium should elapse before blood is drawn, if a valid prothrombin time is to be obtained. When the oral anticoagulant shows full effect and prothrombin activity is in the desired therapeutic range, heparin sodium may be discontinued and therapy continued with the oral anticoagulant.

Therapeutic Anticoagulant Effect with Full-Dose Heparin.

Although dosage must be adjusted for the individual patient according to the results of suitable laboratory tests, the following dosage schedules may be used as guidelines:

METHOD OF ADMINISTRATION	FREQUENCY	RECOMMENDED DOSE (Based on 150 lb. (68 kg.) patient)
Deep Subcutaneous (Intrafat) Injection	Initial Dose	5,000 units by I.V. injection followed by 10,000-20,000 units of a concentrated solution, subcutaneously
	Every 8 hours (or)	8,000-10,000 units of a concentrated solution
	Every 12 hours	15,000-20,000 units of a concentrated solution
Intermittent Intravenous Injection	Initial Dose	10,000 units, either undiluted or in 50-100 ml. isotonic sodium chloride injection
	Every 4 to 6 hours	5,000-10,000 units, either undiluted or in 50-100 ml. isotonic sodium chloride injection
Intravenous Infusion	Initial Dose	5,000 units by I.V. injection
	Continuous	20,000-40,000 units in 1,000 ml. of isotonic sodium chloride solution for infusion/day

1. By deep subcutaneous (intrafat) injection. After an initial I.V. injection of 5,000 units, inject 10,000 to 20,000 units of a concentrated heparin sodium solution subcutaneously, followed by 8,000 to 10,000 units of a concentrated solution subcutaneously every eight hours, or 15,000 to 20,000 units of a concentrated solution every twelve hours. A different site should be used for each injection to prevent the development of a massive hematoma.

2. By intermittent intravenous injection. 10,000 units initially, then 5,000 to 10,000 units every four to six hours. These amounts may be given either undiluted or diluted with 50 to 100 ml. of isotonic sodium chloride injection.

3. By continuous intravenous infusion. After an initial I.V. injection of 5,000 units of heparin sodium, add 20,000 to 40,000 units to 1,000 ml. of isotonic sodium chloride solution for infusion. For most patients, the rate of flow should be adjusted to deliver approximately 20,000 to 40,000 units in 24 hours.

Surgery of the Heart and Blood Vessels: Patients undergoing total body perfusion for open heart surgery should receive an initial dose of not less than 150 units of heparin sodium per kilogram of body weight. Frequently, a dose of 300 units of heparin sodium per kilogram of body weight is used for procedures estimated to last less than 60 minutes; or 400 units per kilogram for those estimated to last longer than 60 minutes.

Low-Dose Prophylaxis of Postoperative Thromboembolism: A number of well-controlled clinical trials have demonstrated that low-dose heparin prophylaxis, given just prior to and after surgery, will reduce the incidence of postoperative deep vein thrombosis in the legs, as measured by the I-125 fibrinogen technique and venography, and of clinical pulmonary embolism. The most widely used dosage has been 5,000 units 2 hours before surgery and 5,000 units every 8 to 12 hours thereafter for 7 days or until the patient is fully ambulatory, whichever is longer. The heparin is given by deep subcutaneous injection in the arm or abdomen with a fine needle (25-26 gauge) to minimize tissue trauma. A concentrated solution of heparin sodium is recommended. Such prophylaxis should be reserved for patients over 40 undergoing major surgery. Patients with bleeding disorders, those having neuro-

surgery, spinal anesthesia, eye surgery, or potentially sanguinous operations should be excluded, as well as patients receiving oral anticoagulants or platelet-active drugs (see WARNINGS). The value of such prophylaxis in hip surgery has not been established. The possibility of increased bleeding during surgery or postoperatively should be borne in mind. If such bleeding occurs, discontinuance of heparin and neutralization with protamine sulfate is advisable. If clinical evidence of thromboembolism develops despite low-dose prophylaxis, full therapeutic doses of anticoagulants should be given unless contraindicated. All patients should be screened prior to heparinization to rule out bleeding disorders, and monitoring should be performed with appropriate coagulation tests just prior to surgery. Coagulation test values should be normal or only slightly elevated. There is usually no need for daily monitoring of the effect of low-dose heparin in patients with normal coagulation parameters.

Extracorporeal Dialysis Use: Follow equipment manufacturer's operating directions carefully.

Blood Transfusion: Addition of 400 to 600 U.S.P. units per 100 ml. of whole blood. Usually, 7,500 U.S.P. units of heparin sodium are added to 100 ml. of Sterile Sodium Chloride Injection (or 75,000 U.S.P. units per 1,000 ml. of Sterile Sodium Chloride Injection) and mixed, and from this sterile solution, 6 to 8 ml. is added per 100 ml. of whole blood. Leukocyte counts should be performed on heparinized blood within two hours after addition of the heparin. Heparinized blood should not be used for isoagglutinin, complement, erythrocyte fragility tests, or platelet counts.

Laboratory Samples: Addition of 70 to 150 units of heparin sodium per 10 to 20 ml. sample of whole blood is usually employed to prevent coagulation of the sample. See comments under "Blood Transfusion".

OVERDOSAGE: Protamine sulfate (1% solution) by slow infusion will neutralize heparin. No more than 50 mg. should be given very slowly, in any 10 minute period. Each mg. of protamine sulfate neutralizes approximately 100 U.S.P. units of heparin (or 1.0 to 1.5 mg. neutralizes approximately 1.0 mg. of heparin). Heparins derived from various animal sources require different amounts of protamine sulfate for neutralization. This fact is of most importance during procedures of regional heparinization, including dialysis.

Decreasing amounts of protamine are required as time from last heparin injection increases. Thirty minutes after a dose of heparin, approximately 0.5 mg. of protamine sulfate is sufficient to neutralize each 100 units of administered heparin. Blood or plasma transfusions may be necessary; these dilute but do not neutralize heparin.

HOW SUPPLIED:

Heparin Sodium Injection, U.S.P. (Derived from Porcine Intestinal Mucosa) is available in the following potencies and sizes:

1 ml., 10 ml. and 30 ml. vials - 1,000 U.S.P. Units per ml.
Each ml. contains: Heparin Sodium 1,000 U.S.P. units, 9 mg. of Sodium Chloride, 1.5% Benzyl Alcohol as preservative and sufficient Water for Injection to volume.

1 ml. and 10 ml. Vial - 5,000 U.S.P. units per ml.
Each ml. contains: Heparin Sodium 5,000 U.S.P. units, 6 mg. Sodium Chloride, 1.5% Benzyl Alcohol as preservative and sufficient Water for Injection to volume.

1 ml., 4 ml., 5 ml. and 10 ml. - 10,000 U.S.P. units per ml.
Each ml. contains: Heparin Sodium 10,000 U.S.P. units, 4.5 mg. Sodium Chloride, 1.5% Benzyl Alcohol as preservative and sufficient Water for Injection to volume.

1 ml., 2 ml. and 5 ml. - 20,000 U.S.P. Units per ml.
Each ml. contains: Heparin Sodium 20,000 U.S.P. Units, 1.5% Benzyl Alcohol as preservative and sufficient Water for Injection to volume.

Heparin Sodium Injection, U.S.P. (Derived from Beef Lung) is available in the following potencies and sizes:

1 ml., 10 ml. and 30 ml. Vials - 1,000 U.S.P. Units per ml.
Each ml. contains: Heparin Sodium 1,000 U.S.P. Units, 9 mg. of Sodium Chloride, 1.5% Benzyl Alcohol as preservative and sufficient Water for Injection to volume.

1 ml. Vials - 5,000 U.S.P. Units per ml.
Each ml. contains: Heparin Sodium 5,000 U.S.P. Units, 6 mg. Sodium Chloride, 1.5% Benzyl Alcohol as preservative and sufficient Water for Injection to volume.

1 ml. and 4 ml. vials - 10,000 U.S.P. Units per ml.
Each ml. contains: Heparin Sodium 10,000 U.S.P. Units, 4.5 mg. Sodium Chloride, 1.5% Benzyl Alcohol as preservative and sufficient Water for Injection to volume.

(Other potencies and sizes on request.)

Sodium Hydroxide or Hydrochloric Acid may be added to adjust pH.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by: Lypho-Med, Inc., Chicago, Illinois 60651
Issued or Revised: November, 1977
Insert No. 50-05

Vial Labeling for 1 ml., 1,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

1965 Rec'd 12-6-71
2-10-78

NDC 0469-0913-00 Vial
SODIUM INJECTION
0 USP Units/ml.
osal) I.V.-Subc.
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See Insert
Mfd. by
LYPHO-MED, INC.

APPROVED

Sterile 1 ml. NDC 0469-0913-00 Vial
SODIUM INJECTION
USP Units/ml.
Porcine Mucosal I.V.-Subc.
Caution: Federal law prohibits dispensing without prescription. See Insert
Mfd. by
LYPHO-MED, INC.

Box Labeling for 1 ml., 1,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

Labeling: 12-6-77

Brkelly 2-10-78

x1 ml. **NDC** 0469-0913-03 Multiple Dose Vials
N SODIUM INJECTION 1,000 USP Units/ml.
erived from Porcine Intestinal Mucosa)
contains: Heparin Sodium 1,000 USP units; cohol 15 mg.; Sodium Chloride 9 mg.; water on q.s. NaOH, HCl to adjust pH if necessary.
OVED
Subc. Use Store at room temperature
Federal law prohibits dispensing without prescription.
See Insert
Mfd. by LYPHO-MED, INC. Chicago, IL 60651
LOT
Exp.

Sterile 25x1 ml. **NDC** 0469-0913-03 Multiple Dose Vials
HEPARIN SODIUM INJECTION 1,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
Each ml. contains: Heparin Sodium 1,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 9 mg.; water for Injection q.s. NaOH, HCl to adjust pH if necessary.
APPROVED
For I.V. or Subc. Use **Store at room temperature**
Caution: Federal law prohibits dispensing without prescription.
See Insert
Mfd. by LYPHO-MED, INC. Chicago, IL 60651
LOT
Exp.

Vial Labeling for 10 ml., 1,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

Labeling: 12-677

NDC 0469-0913-30

Sterile 10 ml.
Multiple Dose Vial

HEPARIN SODIUM
INJECTION
(Porcine Mucosal)
1,000 USP Units/ml.

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

For I.V. or Subc. Use

Caution: Federal law prohibits dispensing without prescription. See Insert

Store at room temperature

Each ml contains: Heparin Sodium 1,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 9 mg.; water for injection q.s. NaOH, HCl to adjust pH if necessary.

Exp.

LOT

APPROVED

NDC 0469-0913-30

Sterile 10 ml.
Multiple Dose Vial

HEPARIN SODIUM
INJECTION
(Porcine Mucosal)
1,000 USP Units/ml.

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

For I.V. or Subc. Use

Caution: Federal law prohibits dispensing without prescription. See Insert

Store at room temperature

Box Labeling for 10 ml., 1,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

Labeling: Orig
No: 17-651 12-6-77
By Walls 2107

x10 ml. **NDC** 0469-0913-33 Multiple Dose Vials
IN SODIUM INJECTION 1,000 USP Units/ml.
Derived from Porcine Intestinal Mucosa)
contains: Heparin Sodium 1,000 USP units; lcohol 15 mg.; Sodium Chloride 9 mg.; water ion q.s. NaOH, HCl to adjust pH if necessary.
Store at room temperature
Federal law prohibits dispensing without prescription.
See Insert
MFD. by
LYPHO-MED, INC.
LOT
Exp.

Sterile 25x10 ml. **NDC** 0469-0913-33 Multiple Dose Vials
HEPARIN SODIUM INJECTION 1,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
Each ml. contains: Heparin Sodium 1,000 USP units; Benzyl [illegible] mg.; Sodium Chloride 9 mg.; water for injection q.s. NaOH, HCl to adjust pH if necessary.
For I.V. or Subc. Use
Store at room temperature
Caution: Federal law prohibits dispensing without prescription.
See Insert
MFD. by
LYPHO-MED, INC.
LOT
Exp.

APPROVED

Box Labeling for 10 ml., 1,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

NDC 0469-0913-30

Sterile 10 ml.
Multiple Dose Vial

HEPARIN SODIUM INJECTION

(Porcine Mucosal)
1,000 USP Units/ml.

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

Each ml. contains: Heparin Sodium 1,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 9 mg.; water for injection q.s. NaOH, HCl to adjust pH if nec. See Insert **Caution:** Federal law prohibits dispensing without prescription. **For I.V. or Subc. Use** Store at room temperature

Exp.

LOT

APPROVED

NDC 0469-0913-30

Sterile 10 ml.
Multiple Dose Vial

HEPARIN SODIUM INJECTION

(Porcine Mucosal)
1,000 USP Units/ml.

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

Each ml. contains: Heparin Sodium 1,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 9 mg.; water for injection q.s. NaOH, HCl to adjust pH if nec. See Insert **Caution:** Federal law prohibits dispensing without prescription. **For I.V. or Subc. Use** Store at room temperature

APPROVED

DRG 12-6-77

Vial Labeling for 30 ml., 1,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
(Derived from Porcine Intestinal Mucosa)

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2-10-78

469-0913-50
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...d from Porcine
...inal Mucosa)
USP Units/ml.

Mfd. by ...MED, INC. ...IL 60651

For I.V. or Subc. Use
Store at room temperature
Caution: Federal law prohibits dispensing without prescription.

Each ml. contains: Heparin Sodium 1,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 9 mg.; water for injection q.s. Hydrochloric Acid or Sodium Hydroxide to adjust pH if necessary.

LOT

Exp.

See Insert

NDC 0469-0913-50
Sterile 30 ml.
Multiple Dose Vial

APPROVED

HEPARIN SODIUM
INJECTION
(Derived from Porcine
Intestinal Mucosa)
1,000 USP Units/ml.

Mfd. by
LYPHOMED, INC.
Chicago, IL 60651

For I.V. or Subc. Use
Store at room temperature
Caution: Federal law prohibits dispensing without prescription.

Box Labeling for 30 ml., 1,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

Rec'd. 12-6-77

) ml. **NDC** 0469-0913-53 Multiple Dose Vials
SODIUM INJECTION 1,000 USP Units/ml.
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ol 15 mg.; Sodium Chloride 9 mg.; water
q.s. NaOH, HCl to adjust pH if necessary.
Sub. Use. Store at room temperature
leral law prohibits dispensing without pre-
See Insert

MFD. BY
LYPHO-MED, INC.
Chicago, IL 60651

LOT
Exp.

Sterile 25x30 ml. **NDC** 0469-0913-53 Multiple Dose Vials
HEPARIN SODIUM INJECTION 1,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
Each ml. contains: Heparin Sodium 1,000 USP units; Phenol, Alcohol 15 mg.; Sodium Chloride 9 mg.; water for injection q.s. NaOH, HCl to adjust pH if necessary.
For I.V. or Subc. Use **Store at room temperature**
Caution: Federal law prohibits dispensing without prescription.
See Insert

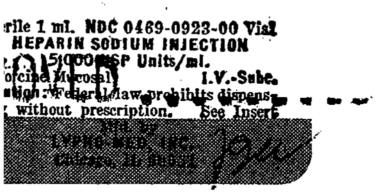
APPROVED

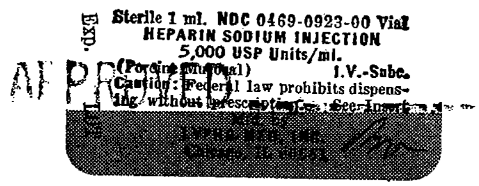
MFD. BY
LYPHO-MED, INC.
Chicago, IL 60651

LOT
Exp.

Vial Labeling for 1 ml., 5,000 U.S.P. units/ml
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

Orig 12-6-77
P Wolter 2-10-78





Box Labeling for 1 ml., 5,000 U.S.P. Units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

ml. **NDC** 0469-0923-03 Multiple Dose Vials
SODIUM INJECTION 5,000 USP Units/ml.
ived from Porcine Intestinal Mucosa)
ntains: Heparin Sodium 5,000 USP units;
ol, 15 mg.; Sodium Chloride 6 mg.; water
q.s. NaOH, HCl to adjust pH if necessary.
Subc. Use **Store at room temperature**
deral law prohibits dispensing without pre-
See Insert

[redacted] Exp.

Sterile 25x1 ml. **NDC** 0469-0923-03 Multiple Dose Vials
HEPARIN SODIUM INJECTION 5,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
Each ml. contains: Heparin Sodium 5,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 6 mg.; water for injection q.s. NaOH, HCl to adjust pH if necessary.
For I.V. or Subc. Use **Store at room temperature**
Caution: Federal law prohibits dispensing without prescription.
See Insert

LOT [redacted] Exp.

Vial Labeling for 10 ml., 5,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

Orig

Labeling

NDA No: 17-651 12-6-77

Approved: P. Walters 2-10-78

NDC 0469-0923-30

Sterile 10 ml.
Multiple Dose Vial

HEPARIN SODIUM
INJECTION
(Porcine Mucosal)
5,000 USP Units/ml.

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

For I.V. or Subc. Use
Caution: Federal law prohibits dispensing without prescription. See Insert
Store at room temperature

Each ml contains: Heparin Sodium 5,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 6 mg.; water for injection q.s. NaOH, HCl to adjust pH if necessary.

Exp.

LOT

NDC 0469-0923-30

Sterile 10 ml.
Multiple Dose Vial

HEPARIN SODIUM
INJECTION
(Porcine Mucosal)
5,000 USP Units/ml.

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

For I.V. or Subc. Use
Caution: Federal law prohibits dispensing without prescription. See Insert
Store at room temperature

APPROVED

Box Labeling for 10 ml., 5,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

5x10 ml. **NDC** 0469-0923-33 Multiple Dose Vials
IN SODIUM INJECTION 5,000 **USP Units/ml.**
Derived from Porcine Intestinal Mucosa)
. contains: Heparin Sodium 5,000 USP units;
Alcohol 15 mg.; Sodium Chloride 6 mg.; water
NaOH, HCl to adjust pH if necessary.
or Subc. Use **Store at room temperature**
Federal law prohibits dispensing without pre-
See Insert

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

LOT

Sterile 25x10 ml. **NDC** 0469-0923-33 Multiple Dose Vials
HEPARIN SODIUM INJECTION 5,000 **USP Units/ml.**
(Derived from Porcine Intestinal Mucosa)
Each vial contains: Heparin Sodium 5,000 USP units;
Benzyl Alcohol 15 mg.; Sodium Chloride 6 mg.; water
for injection q.s. NaOH, HCl to adjust pH if necessary.
For I.V. or Subc. Use **Store at room temperature**
Caution: Federal law prohibits dispensing without pre-
scription.
See Insert

Exp.

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

LOT

Box Labeling for 10 ml., 5,000 U.S.P. Units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

NDC 0469-0923-30

Sterile 10 ml.
Multiple Dose Vial

HEPARIN
SODIUM
INJECTION

(Porcine Mucosal)

5,000 USP Units/ml.

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

Each ml. contains: Heparin Sodium 5,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 6 mg.; water for injection q.s. NaOH, HCl to adjust pH if nec. See Insert
Caution: Federal law prohibits dispensing without prescription. **For I.V. or Subc. Use**
Store at room temperature

Exp.

LOT

NDC 0469-0923-30

Sterile 10 ml.
Multiple Dose Vial

HEPARIN
SODIUM
INJECTION

(Porcine Mucosal)

5,000 USP Units/ml.

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

Each ml. contains: Heparin Sodium 5,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 6 mg.; water for injection q.s. NaOH, HCl to adjust pH if nec. See Insert
Caution: Federal law prohibits dispensing without prescription. **For I.V. or Subc. Use**
Store at room temperature

APPROVED

APPROVED

Vial Labeling for 1 ml., 10,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

Orig 7-26-71
1765
Supp 2-10-78

ml. NDC 0469-0933-00 Vial
ARIN SODIUM INJECTION
0,000 USP Units/ml.
Mucosal) I.V.-Subc.
Federal law prohibits dispens-
out prescription. See Insert
Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

APPROVED

Exp.
LOT

Sterile 1 ml. NDC 0469-0933-00 Vial
HEPARIN SODIUM INJECTION
10,000 USP Units/ml.
(Porcine Mucosal) I.V.-Subc.
Caution: Federal law prohibits dispens-
ing without prescription. See Insert
Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

Box Labeling for 1 ml., 10,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

12-6-77
P.J. Walter 2-10-78

5x1 ml. **NDC** 0469-0933-03 Multiple Dose Vials
IN SODIUM INJECTION 10,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
. contains: Heparin Sodium 10,000 USP units: Alcohol 15 mg.; Sodium Chloride 4.5 mg.; water [illegible] HCl to adjust pH if necessary.
PROVED
For Subc. Use Store at room temperature
Federal law prohibits dispensing without pre-
See Insert

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

Exp.

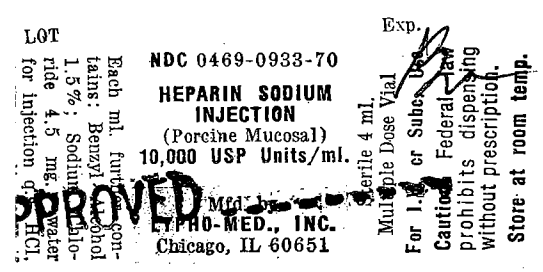
Sterile 25x1 ml. **NDC** 0469-0933-03 Multiple Dose Vials
HEPARIN SODIUM INJECTION 10,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
APPROVED
Each ml. contains: Heparin Sodium 10,000 USP units: Benzyl Alcohol 15 mg.; Sodium Chloride 4.5 mg.; water for injection q.s. NaOH, HCl to adjust pH if necessary.
For I.V. or Subc. Use **Store at room temperature**
Caution: Federal law prohibits dispensing without pre-
See Insert

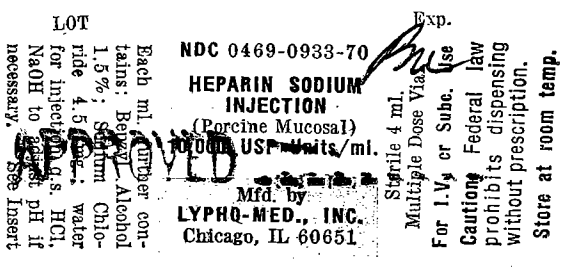
LOT

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

Exp.

Vial Labeling for 4 ml., 10,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa





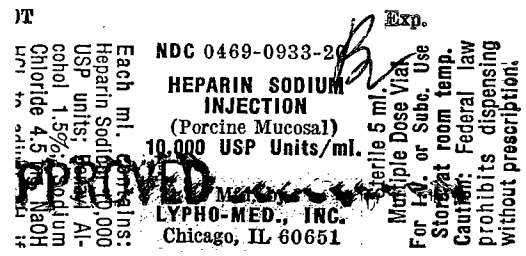
Box Labeling for 4 ml., 10,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

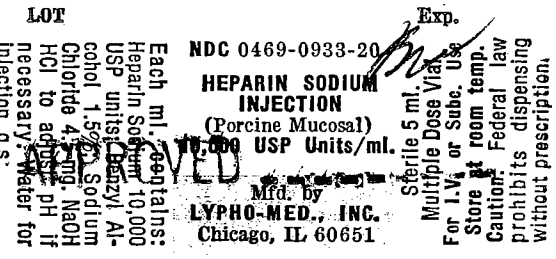
12-6-77
12-65
Approved 2-10-78

5x4 ml. **NDC 0469-0933-73** Multiple Dose Vials
HEPARIN INJECTION 10,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
PROVISIONAL
Each ml. contains: Heparin Sodium 10,000 USP units; Benzyl Alcohol 1% mg.; Sodium Chloride 4.5 mg.; water for injection q.s. NaOH, HCl to adjust pH if necessary.
For I.V. or Subc. Use **Store at room temperature**
Caution: Federal law prohibits dispensing without prescription. **See Insert**
LOT Mfd. by **LYPHO-MED, INC.** Chicago, IL 60651 Exp.

Sterile 25x4 ml. **NDC 0469-0933-73** Multiple Dose Vials
SODIUM HEPARIN INJECTION 10,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
APPROVED
Each ml. contains: Heparin Sodium 10,000 USP units; Benzyl Alcohol 1% mg.; Sodium Chloride 4.5 mg.; water for injection q.s. NaOH, HCl to adjust pH if necessary.
For I.V. or Subc. Use **Store at room temperature**
Caution: Federal law prohibits dispensing without prescription. **See Insert**
LOT Mfd. by **LYPHO-MED, INC.** Chicago, IL 60651 Exp.

Vial Labeling for 5 ml., 10,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa





Box Labeling for 5 ml., 10,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

17-651 12-6-77 Heparin 2-10-78

. **NDC** 0469-0933-23 Multiple Dose Vials
'ARIN INJECTION 10,000 USP Units/ml.
d from Porcine Intestinal Mucosa)
ains: Heparin Sodium 10,000 USP units;
15 mg.; Sodium Chloride 4.5 mg.; water
s. NaOH, HCl to adjust pH if necessary.
OVED . Store at room temperature
al law prohibits dispensing without pre-
See Insert

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

LOT
Exp.

Sterile 25x5 ml. **NDC** 0469-0933-23 Multiple Dose Vials
SODIUM HEPARIN INJECTION 10,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)

APPROVED

Each ml. contains: Heparin Sodium 10,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 4.5 mg.; water for injection q.s. NaOH, HCl to adjust pH if necessary.
For I.V. or Subc. Use **Store at room temperature**
Caution: Federal law prohibits dispensing without prescription.
See Insert

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

LOT
Exp.

Box Labeling for 5 ml., 10,000 U.S.P. Units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

12-6-71

NDC 0469-0933-20

Sterile 5 ml.
Multiple Dose Vial

HEPARIN SODIUM INJECTION
(Porcine Mucosal)
10,000 USP Units/ml.

I.V. or Subc. use

Mfd. by
LYPHO-MED., INC.
Chicago, IL 60651

APPROVED

Each ml. contains: Heparin Sodium 10,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 4.5 mg.; water for injection q.s. Hydrochloric Acid or Sodium Hydroxide to adjust pH if necessary. **Store at room temp.** **Caution:** Federal law prohibits dispensing without prescription. See Insert

Exp.

LOT

NDC 0469-0933-20

Sterile 5 ml.
Multiple Dose Vial

HEPARIN SODIUM INJECTION
(Porcine Mucosal)
10,000 USP Units/ml.

I.V. or Subc. use

Mfd. by
LYPHO-MED., INC.
Chicago, IL 60651

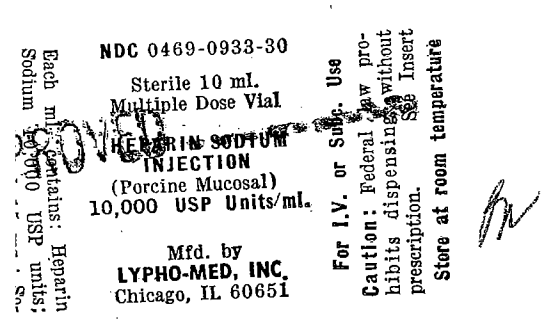
APPROVED

Each ml. contains: Heparin Sodium 10,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 4.5 mg.; water for injection q.s. Hydrochloric Acid or Sodium Hydroxide to adjust pH if necessary. **Store at room temp.** **Caution:** Federal law prohibits dispensing without prescription. See Insert

Exp.

LOT

Vial Labeling for 10 ml., 10,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa



Box Labeling for 10 ml., 10,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

10 ml. **NDC 0469-0933-33** Multiple Dose Vials
HEPARIN INJECTION 10,000 USP Units/ml.
erived from Porcine Intestinal Mucosa)
contains: Heparin Sodium 10,000 USP units; ohol 15 mg.; Sodium Chloride 4.5 mg.; water on q.s. NaOH, HCl to adjust pH if necessary.
...se Store at room temperature
...w prohibits dispensing without pre- See Insert
Exp. Mfd. by LYPHO-MED, INC. Chicago, IL 60651 LOT

Sterile 25x10 ml. **NDC 0469-0933-33** Multiple Dose Vials
SODIUM HEPARIN INJECTION 10,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
Each ml. contains: Heparin Sodium 10,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 4.5 mg.; water for injection q.s. NaOH, HCl to adjust pH if necessary.
For I.V. or Subc. Use **Store at room temperature**
Caution: Federal law prohibits dispensing without prescription. See Insert
Exp. Mfd. by LYPHO-MED, INC. Chicago, IL 60651 LOT

Box Labeling for 10 ml., 10,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

12-6-77
Approved 2-10-78

NDC 0469-0933-30

Sterile 10 ml.
Multiple Dose Vial

HEPARIN SODIUM INJECTION

(Porcine Mucosal)
10,000 USP Units/ml.

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

Each ml. contains: Heparin Sodium 10,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 4.5 mg.; water for injection q.s. NaOH, HCl to adjust pH if nec. See Insert **Caution:** Federal law prohibits dispensing without prescription. **For I.V. or Subc. Use** Store at room temperature

EXPIRATION DATE **LOT NO.**

APPROVED

NDC 0469-0933-30

Sterile 10 ml.
Multiple Dose Vial

HEPARIN SODIUM INJECTION

(Porcine Mucosal)
10,000 USP Units/ml.

Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

Each ml. contains: Heparin Sodium 10,000 USP units; Benzyl Alcohol 15 mg.; Sodium Chloride 4.5 mg.; water for injection q.s. NaOH, HCl to adjust pH if nec. See Insert **Caution:** Federal law prohibits dispensing without prescription. **For I.V. or Subc. Use** Store at room temperature

EXPIRATION DATE **LOT NO.**

APPROVED

Vial Labeling for 1 ml., 20,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

Label
Orig 17-651 12-6-77
Piotto
2-10-78

ROVED

EXP. LOT

Sterile 1 ml. NDC 0469-0943-00 Vial
HEPARIN SODIUM INJECTION
20,000 USP Units/ml.
(Porcine Mucosal) I.V.-Subc.
Caution: Federal law prohibits dispens-
ing without prescription. See [illegible]
Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

APPROVED

EXP. LOT

Sterile 1 ml. NDC 0469-0943-00 Vial
HEPARIN SODIUM INJECTION
20,000 USP Units/ml.
(Porcine Mucosal) I.V.-Subc.
Caution: Federal law prohibits dispens-
ing without prescription. See Insert
Mfd. by
LYPHO-MED, INC.
Chicago, IL 60651

Box Labeling for 1 ml., 20,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

12-6-91
2-10-92

25x1 ml. **NDC** 0469-0943-03 Multiple Dose Vials
ARIN SODIUM INJECTION 20,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
ml. contains: Heparin Sodium 20,000 USP Units;
l Alcohol 15 mg. Water for injection q.s. NaOH,
adjust pH if nec. I.V. or Subc. Use See Insert
Federal law prohibits dispensing without
iption. **Store at room temperature.**

APPROVED

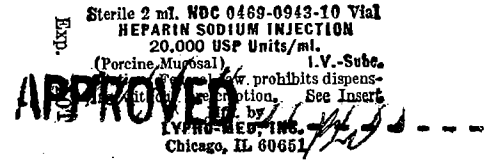
0T **Mfd. by**
LYPHO-MED, INC.
Chicago, IL 60651
Exp.

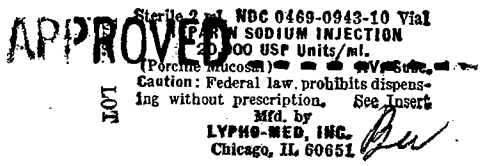
Sterile 25x1 ml. **NDC** 0469-0943-03 Multiple Dose Vials
HEPARIN SODIUM INJECTION 20,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
Each ml. contains: Heparin Sodium 20,000 USP Units;
Benzyl Alcohol 15 mg. Water for injection q.s. NaOH,
HCl to adjust pH if nec. I.V. or Subc. Use See Insert
Caution: Federal law prohibits dispensing without
prescription. **Store at room temperature.**

APPROVED

L0T **Mfd. by**
LYPHO-MED, INC.
Chicago, IL 60651
Exp.

Vial Labeling for 2 ml., 20,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa





Box Labeling for 2 ml., 20,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

12-4-77

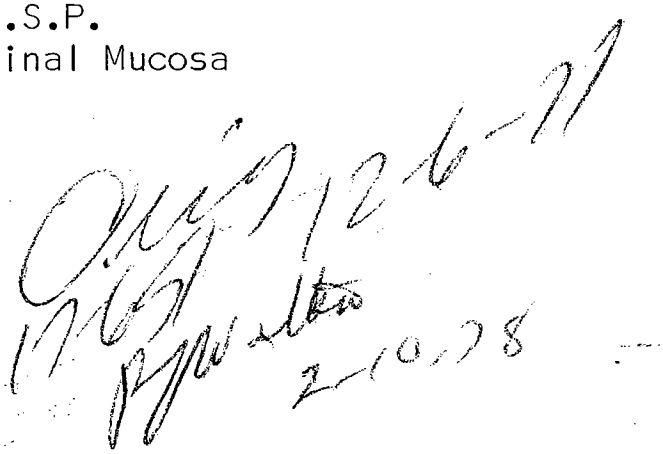
x2 ml. **NDC 0469-0943-13** Multiple Dose Vials
IN SODIUM INJECTION 20,000 USP Units/ml.
Derived from Porcine Intestinal Mucosa)
contains: Heparin Sodium 20,000 USP Units;
lcohol 15 mg. Water for injection q.s. NaOH,
just pH if nec. I.V. or Subc. Use See Insert
APPROVED
Caution: Federal law prohibits dispensing without
Store at room temperature.

LOT Mfd. by **LYPHO-MED, INC.** Chicago, IL 60651 Exp.

Sterile 25x2 ml. **NDC 0469-0943-13** Multiple Dose Vials
HEPARIN SODIUM INJECTION 20,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
Each ml. contains: Heparin Sodium 20,000 USP Units;
Benzyl Alcohol 15 mg. Water for injection q.s. NaOH,
HCl to adjust pH if nec. I.V. or Subc. Use See Insert
APPROVED
Caution: Federal law prohibits dispensing without
prescription. **Store at room temperature.**

LOT Mfd. by **LYPHO-MED, INC.** Chicago, IL 60651 Exp.

Vial Labeling for 5 ml., 20,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa



NDC 0469-0943-20
HEPARIN SODIUM INJECTION
(Porcine Mucosal)
20,000 USP Units/ml.
Mfd. by
LYPHO-MED., INC.
Chicago, IL 60651

Sterile 5 ml.
Multiple Dose Vial
For I.V. or Subc. Use
Caution: Federal law prohibits dispensing without prescription.
Store at room temp.

Each ml. contains: Heparin Sodium 20,000 USP Units; Benzyl Alcohol 9.45 mg. Water for injection q.s. NaOH, HCl to adjust pH if nec. See insert

Exp.

LOT

APPROVED

NDC 0469-0943-20
HEPARIN SODIUM INJECTION
(Porcine Mucosal)
20,000 USP Units/ml.
Mfd. by
LYPHO-MED., INC.
Chicago, IL 60651

Sterile 5 ml.
Multiple Dose Vial
For I.V. or Subc. Use
Caution: Federal law prohibits dispensing without prescription.
Store at room temp.

Box Labeling for 5 ml., 20,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

12-6-77
12-6-77
Approved 2-10-78

25x5 ml. **NDC** 0469-0943-23 Multiple Dose Vials
ARIN SODIUM INJECTION 20,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
contains: Heparin Sodium 20,000 USP Units; Benzyl Alcohol 15 mg. Water for injection q.s. NaOH, HCl to adjust pH if required. I.V. or Subc. Use. See Insert
n: Federal law prohibits dispensing without iption. **Store at room temperature.**

LOT Mfd. by **LYPHO-MED, INC.** Chicago, IL 60651 Exp.

Sterile 25x5 ml. **NDC** 0469-0943-23 Multiple Dose Vials
HEPARIN SODIUM INJECTION 20,000 USP Units/ml.
(Derived from Porcine Intestinal Mucosa)
Each ml. contains: Heparin Sodium 20,000 USP Units; Benzyl Alcohol 15 mg. Water for injection q.s. NaOH, HCl to adjust pH if required. I.V. or Subc. Use. See Insert
Caution: Federal law prohibits dispensing without prescription. **Store at room temperature.**

LOT Mfd. by **LYPHO-MED, INC.** Chicago, IL 60651 Exp.

Box Labeling for 5 ml., 20,000 U.S.P. units/ml.
Heparin Sodium Injection, U.S.P.
Derived from Porcine Intestinal Mucosa

12-6-77
P Woolten
2-10-78

APPROVED

NDC 0469-0943-20

Sterile 5 ml.
Multiple Dose Vial

HEPARIN SODIUM INJECTION

(Porcine Mucosal)

20,000 USP Units/ml.

Mfd. by
LYPHO-MED., INC.
Chicago, IL 60651

Each ml. contains: Heparin Sodium 20,000 USP units; Benzyl Alcohol 15 mg.; water for injection q.s. NaOH, HCl to adjust pH if necessary.
Caution: Federal law prohibits dispensing without prescription.
For I.V. or Subc. Use
See Insert
Store at room temperature

Exp.

LOT

APPROVED

NDC 0469-0943-20

Sterile 5 ml.
Multiple Dose Vial

HEPARIN SODIUM INJECTION

(Porcine Mucosal)

20,000 USP Units/ml.

Mfd. by
LYPHO-MED., INC.
Chicago, IL 60651

Each ml. contains: Heparin Sodium 20,000 USP units; Benzyl Alcohol 15 mg.; water for injection q.s. NaOH, HCl to adjust pH if necessary.
Caution: Federal law prohibits dispensing without prescription.
For I.V. or Subc. Use
See Insert
Store at room temperature

Exp.

LOT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-651

CHEMISTRY REVIEWS

Due to the age of this document,
FOI staff did not locate Chemistry Review #1.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST's REVIEW #2

JUL 16 1975

A. 1. NDA/IND #: 17-651 DATE COMPLETED: June 19, 1975

APPLICANT/SPONSOR: Lypho-Med, Inc.

ADDRESS: Chicago, Illinois 60651

AF#: 4-995

2. PRODUCT NAME(s):

Proprietary: None

Non-proprietary: Sodium Heparin Injection

USAN: Sodium Heparin, U.S.P.

Compendium: Sodium Heparin, U.S.P.

Code name and/or number: None

3. DOSAGE FORM(s) and ROUTE(s) of ADMINISTRATION:

To be administered by subcutaneous and intravenous injections. 1,000, 5,000, 10,000, and 20,000 U.S.P. Units per ml. Rx use only.

4. PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION: Anticoagulant

B. 1. AMENDMENTS: February 10, 1975, responded to our letter of November 1, 1974.
February 11, 1975, Letter of authorization for Joseph Barrows.
May 3, 1975, additional supplier of the raw material Sodium Heparin.
March 25, 1975, FPL & stability data.

2. Supporting M.F. MF [redacted]

MF [redacted]

Letters of authorization are included.

C. REMARKS:

Lypho-Med, Inc. has responded to our letter of November 1, 1974, correcting most of the deficiencies found in the application. However, HFD-322 stated that the firm is not incompliance with CGMP. Sample validation is not considered necessary, since the product is a U.S.P. article, Firm has added an additional supplier of the active ingredient, [redacted]

D. CONCLUSIONS AND/OR RECOMMENDATIONS:

The application is not approvable since deficiencies are still present and an inspection of —— is needed. See draft of chemist's part of letter to applicant.

R/Wolters 7-9-75

R.J. Wolters

CC:
ORIG NDA
HFD-110
HFD-110/CSO
RJWolters/jw/7-9-75
R/D init by J.Langston 6/26/75

J Langston 7/11/75

APPEARS THIS WAY
ON ORIGINAL

E. REVIEW NOTES:

1.&2. Components and Composition: Satisfactory.

Sodium Hydroxide and/or hydrochloric acid may be added to adjust the pH.

3. Synthesis: Additional source of the active ingredient see M.F. ———

4. Raw Material Controls: Satisfactory.

a) New Drug Substance: The complete compendium monograph is performed.

b) Other ingredients: All of the compendia specifications and tests are performed.

5. Other firms: Letters from ——————————— and ——— were submitted. The applicant has submitted an amendment to purchase sodium heparin from ———————————.

6. Container: Letter of authorization from ——————— (M.F.———)

7. Stability: Satisfactory.

Stability data has been submitted for six months. The 18 month expiration date is satisfactory as sodium heparin has a long history with no stability problems.

8. Labeling: Satisfactory form a control standpoint.

9. Establishment Inspection: The memo dated May 16, 1975, from HFD-322 stated that Lypho-Med is not operating in conformance with Current Good Manufacturing Practice [Part 210 (133)]. An inspection of ——— was been requested.

10. Registration: To be determined prior to approval.

11. Form 356H. Complete form 356H is included and signed by Raymond Mesirovc, Ph.D.

"DRAFT OF CHEMIST'S PART, LETTER TO APPLICANT"

We have completed the review of this application and have the following comments:

1. [redacted]

2. Information in report of inspections (two) of your facility by inspectors of this Administration revealed continued significant deviations from current good manufacturing procedures. You may wish to contact the Chicago District after their objections have been corrected.

3. We are deferring comment as to the adequacy of Master File —— as submitted by ———————— pending an establishment inspection of that firm.

APPEARS THIS WAY
ON ORIGINAL

20 OCT 1975

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

CHEMIST'S REVIEW # 3

A. 1. NDA #: 17-651 Date Completed: 10-6-75

Applicant/Sponsor: Lypho-Med, Inc.

Address: Chicago, Illinois 60651

AF # 4-995

2. Product Name(s):

Proprietary: None

Non-proprietary: Sodium Heparin Injection

USAN: Sodium Heparin

Compendium: Heparin Sodium USP XIX

3. Dosage Form(s) and Route(s) of Administration:

To be administered by subcutaneous and intravenous injections, 1,000, 5,000 10,000 and 20,000 USP Units per ml. Rx use only.

4. Pharmacological Category and/or Principal Indication:

Anticoagulant

B. Amendments: September 24, 1975. Submitted in response to our letter of August 5, 1975.

C. Remarks: The amendment dated September 24, 1975, included data relating the amount of ———, to the ——— The NF XIV method was used with slight variations. The amount of ——— was low, satisfactory.

The firm stated that another inspection of their facility was performed by the Chicago District during the period of July 1 to July 15. The firm has responded to Form 2275. Requested HFD 322 to evaluate the current inspection. The establishment inspection report of ——— by HFO 120 stated that the firm is in essential compliance with CGMP. ——— has submitted a revised Master File, which satisfactory details the ———

D. Conclusions and/or Recommendations:

Except for a satisfactory inspection of Lypho-Med, the application is approvable from a manufacturing and controls standpoint.

R. Wolters 10-8-75

R. J. Wolters

cc:
Orig
HFD-110
HFD-110/SCSO
HFD-110/Wolters /dsc/10:7:75

Langston 10/9/75

APPEARS THIS WAY
ON ORIGINAL

DEC 19 1975

Addendum to Chemist's Review # 3

NDA 17-651 Date Completed: 11-11-75

Applicant: Lypho-Med, Inc.

Address: Chicago, Illinois

Product Name: Sodium Heparin Injection USP XIX

Remarks:

HFD-322 has reviewed the establishment inspection report of Lypho-Med and has concluded that the firm is not operating in conformance with Part 211, to assure that products meet the requirements of the Federal Food, Drug and Cosmetic Act.

Conclusions and/or Recommendations:

The application as submitted is deficient from a manufacturing and controls standpoint, in that a satisfactory establishment inspection is required before the application can be approved. Inform the firm of the establishment inspection deficiencies.

R. J. Wolters

cc:
ORIG
HFD-110
HFD-110/SCSO
HFD-110/RJWolters/dsc/12:11:75
R/D init. by: JLangston/dsc/11:12:75

RJWolters 12-12-75

2.1

NOV 12 1976

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #4

DATE COMPLETED: October 19, 1976

A. 1. NDA #: 17-651

APPLICANT: Lypho-Med, Inc.

ADDRESS: Chicago, Illinois 60651

AF #: 4-995

2. PRODUCT NAME(s):

Proprietary: None

Non-proprietary: Heparin Sodium Injection

USAN: Heparin Sodium

Compendium: Heparin Sodium USP XIX

3. DOSAGE FORM(s) AND ROUTE(s) OF ADMINISTRATION:

To be administered by subcutaneous and intravenous injection, 1,000, 5,000, 10,000, and 20,000 USP Units per ml. Rx use only.

4. PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION: Anticoagulant

B. AMENDMENTS: September 28, 1976.

C. REMARKS:

This amendment provides for two additional suppliers of the drug substance, Heparin Sodium. However, information (either by reference to a master file or included in the application) pertaining to the manufacture of the drug substance by either [redacted] or [redacted] was not included. In addition satisfactory inspections of the supplier will be required prior to approval.

With regard to Lypho-Med, Inc. inspection, the firm stated in this amendment that they have had a recent inspection and will submit a response to our letter of December 19, 1975.

D. CONCLUSIONS AND/OR RECOMMENDATIONS:

The application is not approvable from a manufacturing and control standpoint until a satisfactory response to our letter of December 19, 1975, and satisfactory information pertaining to the manufacture of the drug substance as supplied by the new suppliers are received.

R/W Wolters 11/2/76

R. J. Wolters, Chemist

ORIG NDA

HFD-110
HFD-110:CSO
HFD-110:R.J.Wolters:ph:11/1/76
R/D init. by:J.Langston:10/20/76
R.J.Wolters

J Langston 11/2/76

"DRAFT OF CHEMIST'S PART, LETTER TO APPLICANT"

We have completed the review of your New Drug Application and find it inadequate as follows:

1. In addition to the deficiencies stated in our letter of December 19, 1975, the application as amended fails to include a full description of the methods, facilities, and controls used in the manufacture, processing, and packing of the drug substance, Heparin Sodium, by [redacted] and [redacted]

2. Satisfactory inspections of the new suppliers of the drug substance will also be required prior to approval of this application.

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #5

DATE COMPLETED: August 12, 1977

A. 1. NDA #: 17-651

SPONSOR: Lypho-Med, Inc.

ADDRESS: Chicago, Illinois 60651

AF #: 4-995

2. PRODUCT NAME(s):

Proprietary: None

Non-proprietary: Heparin Sodium Injection

USAN: Heparin Sodium

Compendium: Heparin Sodium USP XIX

3. DOSAGE FORM(s) AND ROUTE(s) OF ADMINISTRATION:

To be administered by subcutaneous and intravenous injection. 1,000, 5,000, 10,000 and 20,000 USP Units per ml. Rx use only.

4. PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION: Anticoagulant

B. 1. AMENDMENTS:

February 23, 1977: Submitted in response to the deficient inspection.

July 19 and July 20, 1977: Letters to refer to M.F. ——— and M.F. ———.

August 3, 1977: Submitted in response to the telephone conversations on July 18, 1977 and July 20, 1977.

2. RELATED DOCUMENTS:

M.F. ——, M.F. ——, M.F. —— and M.F. —— and letters of authorization.

C. REMARKS:

The applicant has amended its application to eliminate the remaining deficiencies.

D. CONCLUSIONS AND/OR RECOMMENDATIONS:

The application is approvable from a manufacturing and control standpoint. The container labels will be revised to delete ———— ———— as per the commitment.

R. J. Wolters 8/23/77

R. J. Wolters, Ph.D., Chemist

ORIG NDA
HFD-110
HFD-110:CSO
HFD-110:R.J.Wolters:ph:8/22/77
R/D init. by:J.Langston:8/12/77

J. Langston 8/24/77

E. REVIEW NOTES:

1. and 2. COMPONENTS AND COMPOSITION:

Ingredient	amount per ml			
Heparin Sodium (Porcine)	1,000 Units	5,000 Units	10,000 Units	20,000
Benzyl Alcohol	15 mg	15 mg	15 mg	15 mg
Sodium Chloride	9.0 mg	6.0 mg	4.5 mg	
Sodium Hydroxide or Hydrochloric Acid qs pH	5.0 to 7.5			
Water for Injection qs to	1.0 ml	1.0 ml	1.0 ml	1.0 ml

The new composition was submitted as ——— was remove from the formulation. Satisfactory.

3. SYNTHESIS:

The drug substance will be obtained from ——— in addition to the other suppliers previously listed. M.F. —— satisfactory describes the method of manufacture. Firm has been approved as a supplier for other manufacturers. Satisfactory.

4. MANUFACTURING AND PROCESSING:

The file for the 1 ml vial is 1.2 ml. Satisfactory.

5. CONTAINER:

——— will also supply the rubber stopper as per M.F. ——. Satisfactory.

6. LABELING:

The container labels will be revised to delete the ——— ——— as per commitment. Satisfactory.

7. ESTABLISHMENT INSPECTION:

Memo from HFD-322 dated 7/13/77 states that the firm is operating in comformance with CGMP.

8. REGISTRATION: ———

FEB 10 1978

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

CHEMIST'S REVIEW # 6

A. 1. NDA #: 17-651 Date Completed: 12/6/77

Applicant/Sponsor: Lypho-Med, Inc.
Address: Chicago, Illinois 60651

AF # 4-995

2. Product Name(s):

Proprietary: None

Non-proprietary: Heparin Sodium

USAN: Heparin Sodium

Compendium: Heparin Sodium USP XIX

3. Dosage Form(s) and Route(s) of Administration:

To be administered by subcutaneous and intravenous injection, 1,000, 5,000, 10,000, and 20,000 USP units per ml. Rx use only.

4. Pharmacological Category and/or Principal Indication:

Anticoagulant

B. Amendments: December 6, 1977: Revised container labels and package insert, and deletion of ——— as an outside testing laboratory.

C. Remarks: The November 3, 1977 memo from HFD-322 for NDA 17-979, Lypho-Med beef lung heparin updates the previous inspection memo. It is noted that Lypho-Med has deleted ——— as an outside testing laboratory. Only ——————————— will be used.

D. Conclusions and/or Recommendations: The application is approvable from a manufacturing and control standpoint.

cc: Orig. NDA
HFD-110
HFD-110/RJWolters/ep/12/9/77
R/d init. by: JLangston/12/6/77

R. J. Wolters 12-9-77
R. J. Wolters

J. Langston 12/9/77

E. Review Notes:

1. Other firms:

_____ will be deleted as an outside testing firm.

2. Labeling:

Package insert conforms to the latest labeling guidelines with respect to the technical aspects.

Container labels are satisfactory insofar as the technical aspects are concerned.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-651

PHARMACOLOGY REVIEW

PHARMACOLOGIST'S REVIEW OF NDA 17-651

Sponsor:	Lypho-Med, Inc.
Drug:	Sodium Heparin Injection, U.S.P.
Dosage:	Should be adjusted according to pts. clotting time. Initially, about 10,000 units.
Indications:	Anticoagulant

DMF ———————————. Reference letter of permission enclosed.

Related NDA's:	552, 1623, 3895, 4570, 5264, 5521, 5942, 6047, ——, 7530, 11026, 11219, ——, —— 17029 17033, 17035, 17036, 17037, ——, ——, ——, ——, 17130, 17346, ——, 17486, ——, ——, 17540, ——, ——, ——, ——, ——, ——
Related IND's:	Listing unnecessary.
Standards:	U.S.P. XVIII monograph; FDA smaple labeling guidelines 10/2/72.
Comments:	This drug in widely marketed and its properties are well known to the average physician.

Recommendations:

Applicant should be informed about the more recent sample labeling of 6/20/73. Application is approvable from a Pharmacological viewpoint.

William Van Arsdel, Ph.D.

cc:
Orig. NDA
Dup. NDA
HFD-100
HFD-110
HFD-110/CSO
HFD-102/Aguanno
HFD-110/Arsdel/dmr/10-31-74
init/GarBoHo

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-651

ADMINISTRATIVE DOCUMENTS

SUMMARY OF NDA 17-651

DATE SUMMAY COMPLETED: 9/24/74
NDA #: 17-651
COMPANY: Lypho-Med, Inc.
ADDRESS: Chicago, Illinois 60651
ORIGINAL APPROVAL DATE: N.A.
REVIEWED BY NAS/NRC: Yes

NAME OF DRUG: Trade: Sodium Heparin Injection, U.S.P.

Generic: Sodium Heparin Injection, U.S.P.---- 1,000-5,000-10,000-20,000 U.S.P. Units/ml./ 1-5-10 ml. vials

DOSAGE FORMS AND ROUTE OF ADMINISTRATION: Injections for parenteral use.

CATEGORY OR USE OF DRUG: Anticoagulant agent.

DATE OF NDA: September 10, 1974

REASON FOR SUBMISSION: 'New' NDA

MATERIAL REVIEWED: NDA.

COMMENTS:

From medical point of view this NDA can not be objected. There are approximately 27 'Heparin' NDA's already on market.

However, before approval, the following conditions should be met:

1. The draft labeling to be updated according to DESI 552 (revised) Notice as published in the 37 F.R. of January 12, 1972.

2. Also it has to be in compliance with BD's most recent version of Heparin guidelines. Dated as of June 20, 1973.

3. Prior to the foregoing, chemicals control data should be completely acceptable by HFD-110.

RECOMMENDATIONS:

As outlined above.

A. A. Solymossy, M.D.

cc:
Orig-NDA
Dup-NDA
HFD-100
HFD-110
HFD-110-CSO
HFD-110/Solymossy/fh/9/26/74

NDA 17-651 JUL 16 1975 DATE 2/19/75

IND

FIRM Lypho-Med

DRUG Sodium Heparin Chicago, Illinois

MEMORANDUM OF CONFERENCE

BETWEEN

Dr Raymond Mesirow
Joseph Barrows

AND

Arthur Auer
Robert Wolters
Dr. Solymossy

SUBJECT:

Meeting regarding NDA 17-651 Mr. Barrows distributed their re-submission of 17-651 responding to our deficiency letter.

Dr. Mesirow stated that 6 month stability data would be completed about March 1, 1975, and the firm is ready for another inspection

We will need a satisfactory inspection and stability data.

Robert Wolters

ORIG NDA
HFD-110
HFD-110:CSO
HFD-110:R.Wolters:ph:2/20/75
HFD 110:A Auer

MEMORANDUM

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

JUL 16 1975

TO : DIRECTOR, DIVISION OF CARDIOPULMONARY RENAL DRUG PRODUCTS, HFD-110
ATTN: ROBERT WALTERS

DATE: January 21, 1975

FROM : Acting Chief, Manufacturing Review Branch, HFD-322
Division of Drug Manufacturing

SUBJECT: Recommendation for Disapproval of NDA 17-651, Sodium Heparin Injection

APPLICANT: Lypho-Med, Inc.
Chicago, Illinois

We have evaluated the operations of the above referenced firm, Lypho-Med, as they relate to compliance with Current Good Manufacturing Practice Regulations (21 CFR 133). On the basis of this evaluation, we cannot approve the subject NDA as the firm is not operating in conformance with Part 133 to assure that products meet the requirements of the Federal Food, Drug and Cosmetic Act as to safety, and have the identity and strength, and meet the quality and purity standards which they purport to possess.

Our recommendation for disapproval is based on the findings noted in an EI conducted 2-26-74 through 4-10-74, which include:

Failure to develop and maintain suitable cleaning procedures for containers.

a. _____ used for _____ of vials and closures is not _____. No _____ with _____ _____ is performed.

Failure to establish and maintain an effective stability testing program on products in their finished market containers.

a. There is no written program effectively covering stability testing as the basis for establishing meaningful expiration dates.

Failure to eliminate avenues of possible contamination from sterile fill room.

a. _____
_____.

Failure to assure that components meet established specifications prior to release from quarantine.

a. Raw materials released for use prior to completion of specified tests.

Failure to record test results in a concise manner.

a. Raw materials test data was observed to be recorded on a pad of paper rather than in the bound notebook.

The accuracy of laboratory equipment is not checked on a regular basis.

a. There is no written program to determine the accuracy of _____, etc., at specified time intervals and a record of equipment calibrations is not maintained.

David H. Bryant

David H. Bryant

MEMORANDUM

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

DEC 19 1975

TO : Director, Division of Cardiopulmonary
Renal Drug Products, HFD-110
Attn: Robert Walters

DATE: October 30, 1975

FROM : Acting Chief, Manufacturing Review Branch (HFD-322)
Division of Drug Manufacturing

SUBJECT: Evaluation of NDA 17-651, Sodium Heparin

APPLICANT: Lypho-Med
Chicago, Illinois

MANUFACTURER: Lypho-Med
Chicago, Illinois

We have evaluated the operations of Lypho-Med as they relate to compliance with Current Good Manufacturing Practice Regulations (21 CFR 211) and the referenced New Drug Application. On the basis of this evaluation we conclude that the firm is not operating in conformance with Part 211 to assure that products meet the requirements of the Federal Food, Drug, and Cosmetic Act as to safety, and have the identity and strength, and meet the quality and purity standards for which they purport to possess.

Inspection beginning on 7-1-75 disclosed several critical and serious deviations from CGMPs including:

1. Employees in ——— filling area are not adequately trained in the required techniques.

2. Employees not adequately garbed - hair not covered.

3. Microbiological testing and control of environmental conditions are not performed in accordance with firm's SOP and some test results are not recorded.

4. There are no "action levels" for microbiological environment controls.

5. ——————— agents not tested for effectiveness or identity upon receipt.

6. No data was available regarding the suitability of the product containers.

7. Entries on batch records are changed without explanation or initials of person making change.

David H. Bryant

cc: CHI-DO (HFR-5100)
HFD-110 (RWalters)
HFV-210
HFD-332 (WRobinson)
HFD-322 Log
HFD-322 Firm File
HFD-300 R/F
HFD-110 (NDA Orig)
HFD-110 (NDA Dup)
HFA-226
OAGoldbaum:zr

MEMORANDUM

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

TO : Director, Division of Cardio-Renal Drug Products (HFD-110)
Attn: R. Wolters

DATE: July 13, 1977

FROM : Chief, Manufacturing Review Branch (HFD-322)
Division of Drug Manufacturing

SUBJECT: Approvable NDA 17-651, Heparin Sodium Injection (Porcine Intestines)

APPLICANT: Lypho-Med, Inc.
Chicago, Ill.

We have reevaluated the operations of the referenced applicant as they relate to compliance with Current Good Manufacturing Practice Regulations (21 CFR 211) and the referenced New Drug Application. We conclude that there is no reason to withhold approval of the referenced pending NDA insofar as it relates to this firm and the type of operations as specified in this pending new drug application.

Our evaluation is based in part on an inspection conducted 3/7-4/1/77.

David H. Bryant

David H. Bryant

cc: CHI-DO (HFR-5100)
HFV-234
HFD-322 Firm File
HFD-300 R/F
HFD-110 (NDA Orig)
HFA-224
WABrown:rdj:7/13/77

Summary of Amendment

NDA# 17-651 Date: 9/14-77

Company: Lypho-Med, Inc.
4020 West Division Street
Chicago, Illinois 60651

Key and Date of Amendment: R-----8/3/77

Product: Heparin Sodium Injection, USP

Category: Anticoagulant agent

Reason for Submission: Resubmission of NDA original amendment.

Comments: This amendment consists of manufacturing and controls data. However, the cover letter states: "....3. As requested by MR. Robert Walters, we will delete ——— from our labeling at the next printing."

Since the said request (made by phone on July 18, 1977) our Heparin Sample Labeling has been thoroughly revised and updated, according to current clinical practice, so it is now appropriate for the firm to follow the current Guide-line (8/77).

Recommendation: 1. A copy of the new Heparin Sample Labeling should be sent to the firm in order to update their current labeling.

2. If the foregoing matter is resolved all the conditions listed in the reviewer's prior (9/24/74) summary of NDA 17-651 are met and thus the NDA can be approved.

A. A. Solymossy, M.D.

cc: Orig NDA 17-651
HFD-110
HFD-110:CSO
HFD-110:AASolymossy:is/9-15-77

RECORD OF TELEPHONE CONVERSATION

(Retain pink copy, forward remainder of copies to Management Technician, BD 120)

SUMMARY OF CONVERSATION

I called in response to Dr. Finkel's note, asking that the draft vial label be revised to delete _____ as promised by the applicant but not submitted with the draft "approvable" letter

Mr. Hanuskewsky promised to provide the revised label ASAP.

DATE: 11/3/77

NDA NUMBER: 17-651

IND NUMBER:

CALL INITIATED BY

- ☐ APPLICANT/SPONSOR
- ☒ FDA

NAME OF PRODUCT: Heparin Sodium

NAME OF FIRM: Lypho-Med

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Mike Hanuskewsky

312-342-6170

SIGNATURE: Arthur Elmer

FDH FORM 2587 (9/72)

MEMORANDUM OF (TELEPHONE CONVERSATION)

BETWEEN

Micael Hanushewsky
Director of Regualtory Affairs

AND

Robert Wolters HFD-110-Chemist

NDA 17-656 & 17-970 DATE: 11-14-77

DRUG: Heparin Sodium FIRM: Lypho-Med

SUBJECT: I said that I had received a memo from our Manufacturing Review Branch stating that ——— was not in compliance with CGMP. I asked that he submit a letter deleting ——— as a contract testing lab. After the NDA s are approved he could then submit a supplement to provide for ——— or any other laboratory.

I asked him to submit labeling deleting the ——— ——— as per his phone call from Arthur Auer.

I asked him to clarify the How Supplied section of the package insert for the beef lung heparin as the section includes a reference to the 20,000 USP per ml potency while labels were not submitted.

He said that the package insert was combine for both the porcine and beef heparins and they make a 20,000 USP units per ml potency for porcine heparin. He siad that they will separate the inserts when they revise the insert as per the F.R. announcement of 10-7-77.

R J Wolters 11/22/77
R. J. Wolters, Chemist

cc: Orig NDA's 17-656 & 17-970
HFD-110
HFD-110:CSO
HFD-110:RJWolters:is:11-21-77

SUMMARY BASIS OF APPROVAL

NDA 17-651

APPLICANT: Lypho-Med, Incorporated
4020 West Division Street
Chicago, Illinois 60651

DRUG GENERIC NAME: Heparin Sodium Injection

TRADE NAME: None

I. Indication for use:

Heparin sodium injection is indicated for anticoagulant therapy in prophylaxis and treatment of venous thrombosis and its extension; in low-dose regimen for prevention of postoperative deep venous thrombosis and pulmonary embolism in patients undergoing major abdomino-thoracic surgery who are at risk of developing thromboembolic disease (see DOSAGE AND ADMINISTRATION section); for prophylaxis and treatment of pulmonary embolism; in atrial fibrillation with embolization; for diagnosis and treatment of acute and chronic consumptive coagulopathies (disseminated intravascular coagulation); for prevention of clotting in arterial and cardiac surgery; and for prevention of cerebral thrombosis in evolving stroke.

Heparin is indicated as an adjunct in treatment of coronary occlusion with acute myocardial infarction, and in prophylaxis and treatment of peripheral arterial embolism.

Heparin may also be employed as an anticoagulant in blood transfusions, extracorporeal circulation, dialysis procedures, and in blood samples for laboratory purposes.

II. Dosage Form, Route of Administration and Recommended Dosage.

This injectable drug is intended for intermittent intravenous injection, intravenous infusion or subcutaneous injection. The drug can also be used as an anticoagulant in whole blood or whole body perfusion in the case of open heart surgery or other similar procedures.

The dosage of Sodium Heparin varies with the intended use. Actual dose in anticoagulation therapy is titrated to elevate the clotting time from 2 1/2 to 3 times. For total body perfusion, the dose varies from 150 units per kilogram body weight to 400 units per kilogram. For blood transfusions 400 to 600 units per 100 cc whole blood is used.

The most recently approved package insert should always be consulted for the most up-to-date information on proper use of the drug.

III. MANUFACTURING AND CONTROLS:

A. The drug product is manufactured, packaged and labeled by Lypho-Med, Incorporated from porcine intestinal mucosa. The active principle is extracted and purified by use of standard established procedures.

B. The applicant has sufficient stability data to support the proposed expiration date.

C. This product is tested by the compendial methods appearing in the U.S.P. XIX.

D. Labeling is not false or misleading in any respects and complys with the requirements of the Code of Federal Regulations and the U.S.P. XIX.

E. Evaluation of the establishment inspection dated July 13, 1977, revealed that the firm is in compliance with Current Good Manufacturing Practice Regulations (21 CFR 211).

F. An Environmental Impact Analysis Report was included in the application. The applicant states that there will be little or minimum additional impact on the environment from the manufacture of the drug product as this product is already manufactured by numerous firms. At this time, further considerations are not necessary for approval of this application.

IV. PHARMACOLOGY

The anticoagulant properties of sodium heparin injection USP are widely recognized by pharmacologists. Extensive discussion of the pharmacology of this can be found in most standard reference books in the field.

Heparin is derived from animal tissue (beef or swine mucosa) and must be given by injection because its activity is destroyed in the stomach.

This product was discovered in 1916. The first clinical trials were conducted in 1937.

V. MEDICAL

Heparin Sodium was evaluated by the "Panel on Drugs Used in Hematological Disorders" of the National Academy of Science - National

Research Council (NAS/NRC) and found effective as a well-established anticoagulant with which there has been long and extensive experimental and clinical experience. Suppertive documentation included reference to Jaques, L.B. on Heparin (pp. 33-89) entitled "In Anticoagulant Therapy" published in 1965.

In view of the NAS/NRC panel recommendation; and the established safety experience data, the safety and effectiveness of sodium heparin injection is clinically recognized by practicing physicians and hematologists.

As a result of this wide clinical experience with sodium heparin, we have established model class labeling for the drug. This labeling was followed by the applicant.

VI. The approved package insert is attached.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-651

CORRESPONDENCE

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

Form Approved
OMB No. 57-R0003

17-651

NEW DRUG APPLICATION

LYPHO-MED, INC.

FREEZE DRIED PHARMACEUTICALS

4122-30 W. GRAND AVE., CHICAGO, ILL. 60651
312) 342-6170 · F.D.A. EST. NO. 14-17023

E.D. Belton, M.D., Director
Cardiorenal Division
Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

RE: NEW DRUG APPLICATION
SODIUM HEPARIN INJECTION, U.S.P.
1,000 U.S.P. Units per ml., 5,000 U.S.P. Units per ml., 10,000 U.S.P. Units per ml., and 20,000 U.S.P. Units per ml.
Ref: D.E.S.I. 552, F.R. Vol. 35, No. 208 dated Saturday, October 24, 1970.

Dear Doctor Belton:

Pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act we are submitting herewith a New Drug Application for Sodium Heparin Injection, J.S.P.

Included in this submission are the following:
a) Volume No. 1 - Copy No. 1 (Blue Folder)
b) Volume No. 1 - Copy No. 2 (Red Folder)
c) Volume No. 1 - Copy No. 3 (Yellow Folder)

The labels and package inserts are in draft form and in conformity with the FDA's sample labeling dated October 2, 1972; and the D.E.S.I. guidelines published in the Federal Register of February 10, 1972.

The New Drug Application contains all pertinent data as per the discussion of our consultant, Joseph Barrows, Ph.G. and Alfred A. Solymossy, M.D. of your Division.

Respectfully submitted,
Lypho-Med, Inc.

Raymond Mosiraw, Ph.D.
Vice President

Date

RECEIVED
SEP 18 1972
BUREAU OF DRUGS

A

LYPHO-MED, INC.
FREEZE DRIED PHARMACEUTICALS

4122-30 W. GRAND AVE. CHICAGO, ILL. 60651
(312) 342-6170 • F.D.A. EST. NO. 4-17023

ORIG-NEW CORRES
(C)

ORIGINAL

19-651

February 11, 1975

Richard Crout, M.D. - Bureau of Drugs
Food & Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Dear Doctor Crout:

This letter authorizes Joseph Barrows, Ph.G. to represent our company in matters of drug regulatory affairs, including new drug applications, etc.

Respectfully submitted,

Raymond Mesirow
Vice-President-General Manager

RECEIVED
FEB 19 1975
HFD-110
BUREAU OF DRUGS

a

cc: Joseph Barrows
Gerald M. Freeman

Memo to J. Barrows: This acknowledges our meeting Wednesday, February 19 in Rockville with Drs. Allen and Walters. I will notify you to the contrary if there is any change in plans.

R. Mesirow

Resubmission

NDA AMENDMENT

ORIGINAL

LYPHO-MED, INC.

FREEZE DRIED PHARMACEUTICALS

4122-30 W. GRAND AVE., CHICAGO, ILL. 60651

(312) 342-6170 · F.D.A. EST. NO. 14-17023

R

March 25, 1975

Prior (9/74) labeling is now corrected in accordance with our recommendations. Permit the FPL. AAS/3-31-

E. DeVaughn Belton, M.D., Director
Division of Cardio-Renal Drug Products
Office of Scientific Evaluation,
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Ref: NDA 17-651 (Amendment II)
Product: Sodium Heparin Injection, U.S.P.

Dear Doctor Belton:

As requested in communications subsequent to our new drug application under Section 505 (b)(4), (5) and (6) of the Act, we are herewith forwarding the following information:

1. Certification by ——— that they shall perform the ——— testing of each production batch of the drug and that the methods used in and the facilities and controls used for this program of testing are in conformity with the New Drug Application filed by Lypho-Med, Inc. (Letter enclosed)

2. Final printed form of all current labeling. A total of 12 copies for each potency and size container as well as the package insert are attached. To clarify, all vial and carton labeling is prepared from ——— which are used to produce ———

———

the printing of cartons. The enclosed sheets represent then, ——— ——— of both vial and carton —— and are complete except for completion of the lot number and expiration date.

3. Stability data to substantiate an expiration date proposed for this product. As stated in our previous submissions, we have initiated the testing of production lots after six months storage at ambient temperatures (55°-80°C.). Since our first production lots of this product were manufactured in August, 1974 and were limited to the 1,000 Unit and 5,000 Units/cc. potencies, only these two potencies have been retested. We prepared subsequently our first lot of the 10,000 Units/cc. product in October, 1974 and therefore intend to submit stability data for this potency on or about April 30, 1975. We have not, nor do we anticipate the production of 20,000 Units/cc. material in the near future. The continued testing of each of these potencies shall proceed after 9 months, 12 months, 18 months, 24 months and beyond as elapsed time permits.

RECEIVED MAR 26 1975 HFD-110 FDA

Samples in hfd 106 drug room

MAR 26 1975

LYPHO-MED, INC.
FREEZE DRIED PHARMACEUTICALS
4122-30 W. GRAND AVE., CHICAGO, ILL. 60651
(312) 342-6170 · F.D.A. EST. NO. 14-17023

ORIGINAL
NDA ORIG AMENDMENT

May 3, 1975

Re: NDA 17-651
Sodium Heparin Injection,
U.S.P.
Amendment

E. DeVaughn Belton, M.D., Director
Division of Cardio-Renal Drug Prducts
Office of Scientific Evaluation, Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Dear Doctor Belton:

Pursuant to our NDA 17-067 submission for Sodium Heparin Injection, U.S.P., we wish to amend said application as per the attached amendment.

Respectfully submitted,

LYPHO-MED, INC.
Jerome S. Kernes
Quality Control Director

RECEIVED
MAY 6 1975
HFD-110
BUREAU OF DRUGS

NDA 17-651

AF# 4-995

Lytho-Med, Inc.
Attention: Raymond Mestrow, Ph.D.
4122-30 West Grand Avenue
Chicago, Illinois 60651

5 AUG 1975

Dear Dr. Mestrow:

This is in reference to your New Drug Application dated September 18, 1974 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Sodium Heparin Injection, U.S.P., and to your communications dated February 10, 1975, March 25, 1975 and May 3, 1975.

We have completed our review of your New Drug Application and find it incomplete and inadequate for the following reasons:

1. [redacted]

2. Information and reports of inspections (2) of your facilities by inspectors of this Administration reveal continued significant deviations from good manufacturing practices. You may wish to contact the Chicago District after their objections have been corrected.

Because of these deficiencies, the Application will not be filed as a New Drug Application within the meaning of section 505(b) of the Act. Should you have any questions regarding the reasons for refusing to file this NDA please call: Mr. Arthur Auer, Consumer Safety Officer (301) 443-4730.

Sincerely yours,

E. DeVaughn Belton, M. D.
Director
Division of Cardio-Renal
Drug Products
Bureau of Drugs

cc:
Orig
HFD-110
HFD-110/SCSO
HFD-110/THDavis/ydsc/7-22-75
R/D initialed by: ASolymossy/
7-25-75, RWolters/7-28-75

ORIGINAL

LYPHO-MED, INC.

FREEZE DRIED PHARMACEUTICALS

4122-30 W. GRAND AVE., CHICAGO, ILL. 60651
(312) 342-6170 · F.D.A. EST. NO. 14-17023

September 24, 1975

NDA ORIG AMENDMENT
A
10-2-75

E. DeVaughn Belton, M.D.
Director
Division of Cardio-Renal Drug Products
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: NDA 17-651

Subject: Amendment No. 3

Dear Dr. Belton:

In reference to your letter of August 5 ,1975, I have prepared the enclosed data relating to the _____ used in the production of Sodium Heparin Injection, U.S.P. by Lypho-Med. Although our own data was produced earlier, we were waiting for the laboratory data submitted by the manufacturer, _____ before submitting this amendment.

Item 2. We are currently awaiting a reply by the Chicago District Office to our response to Form 2275, resulting from their inspection of our facility during the period July 1 through July 15th. It is our hope that we will subsequently be found acceptable and meet the requirements for approval of our NDA.

Respectfully submitted,

Jerome S. Kernes
Quality Control Director

RECEIVED
SEP 29 1975
HFD-110
BUREAU OF DRUGS

NDA 17-651
AF 4-995

Lypho-Med, Inc.
Attention: Jerome S. Kernes
4122-30 West Grand Avenue
Chicago, Illinois 60651

DEC 19 1975

Gentlemen:

This is in reference to your New Drug Application dated September 18, 1974, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Sodium Heparin Injection, U.S.P., and to your communication dated September 24, 1975.

We have completed the review of your New Drug Application and find it incomplete and inadequate as a report of the establishment inspection of your facility, as reviewed by our Division of Drug Manufacturing, contains deviations from Current Good Manufacturing Practices including:

1. Employees in ——— filling area are not adequately trained in the required techniques.

2. Employees not adequately garbed - hair not covered.

3. Microbiological testing and control of environmental conditions are not performed in accordance with firm's SOP and some test results are not recorded.

4. There are no "action levels" for microbiological environment controls.

5. ——————— agents not tested for effectiveness or identity upon receipt.

6. No data was available regarding the suitability of the product containers.

7. Entries on batch records are changed without explanation or initials of person making change.

On the basis of this evaluation our Division of Drug Manufacturing concludes that the firm is not operating in conformance with Part 211 to assure that products meet the requirements of the Federal Food, Drug, and Cosmetic Act as to safety, and have the identity and strength, and meet the quality and purity standards for which they purport to possess.

Because of these deficiencies, the Application will not be filed as a New Drug Application within the meaning of section 505(b) of the Act. You may wish to contact the Chicago District after their objections have been corrected.

Sincerely yours,

E. DeVaughn Belton, M. D.
Director
Division of Cardio-Renal
Drug Products
Bureau of Drugs

cc:
ORIG
HFD-110
HFD-110/SCSO
HFD-110/RWolters/dsc/12:11:75
R/D init. by: dLangston/AAuer 11:11:75

IN

ORIGINAL

Lypho-Med, Inc.

a subsidiary of Stone container corporation

FDA. est. no. 14-17023

4020 west Division street
Chicago, Illinois 60651

312. 342 6170

NDA ORIG. AMENDMENT

September 28, 1976

E. DeVaughn Belton, M.D.
Director-Division of Cardio-Renal Drug Products
Department of Health, Education, and Welfare
Public Health Service
Food & Drug Administration
Rockville, Maryland 20852

Dear Dr. Belton:

Enclosed please find an amendment to our NDA 17-651 wherein we are adding two new sources of Heparin Sodium U.S.P. to our application.

In view of our recent inspection, we expect to submit a complete response to your letter of December 19, 1975.

Sincerely yours,

Raymond Mesirow

Raymond Mesirow
Vice President-General Manager

A
Encl.

cc: A. Kolef

RECEIVED
OCT 1 1976
HFD-110
BUREAU OF DRUGS

Lypho-Med, Inc.

a subsidiary of Stone container corporation

FDA. est. no. 14-17023

4020 west Division street
Chicago, Illinois 60651

312. 342 6170

ORIGINAL

NDA ORIG Amendment

4

E.D. Belton, M.D., Director
Cardiorenal Division
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20857

FEB 23 1977

Re: NDA 17-651
SODIUM HEPARIN INJECTION, USP
Your Letter: December 19, 1975

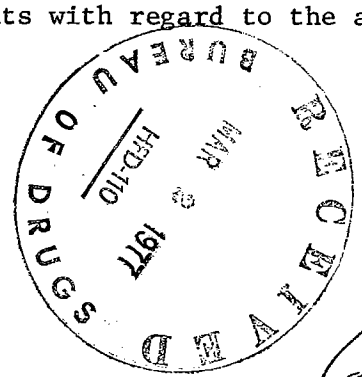
Dear Dr. Belton:

We apologize for the long delay in answering your above referenced letter in regard to our NDA for SODIUM HEPARIN INJECTION due to circumstances beyond my control. Please be advised that we are now in a position to make the following comments with regards to your letter.

It appears that the questions raised in your letter were precipitated by the Federal inspection of Lypho-Med dated July 1, 1975 by investigators Wallis Weiler and Cruz Ruiz of the Chicago district office. On September 12, 1975, an extensive letter of response giving corrective measures, point by point, was sent to Mr. Owen Lamb, the Compliance Officer of the Chicago branch and we fail to understand, at this point, why in your letter of December 19, 1975 these same areas of deficiency were enumerated again.

We wish to assure the Food and Drug Administration that Lypho-Med has and is endeavoring to correct any deficiencies, past or present, which are not in conformity with current good manufacturing practice in accord with Part 133, of Chapter I, Title 21 of the Code of Federal Regulations.

Your comments with regard to the above would be sincerely appreciated at this time.



Respectfully Submitted,
LYPHO-MED, Inc

J.G. Baumann
Regulatory Affairs

PERSONALLY SUBMITTED BY
M. Hanuszkewsky
dup.

Lypho-Med, Inc.

a subsidiary of Stone container corporation

FDA. est. no. 14-17023

4020 west Division street
Chicago, Illinois 60651

RESUBMISSION
NDA ORIG AMENDMENT

August 3, 1977

ACTION:
REVIEWER:
DATE:

Robert J. Temple, M.D., Director
Cardiorenal Division
Office of Scientific Evaluation
BUREAU OF DRUGS
5600 Fishers Lane
Rockville, Maryland 20852

RE: NDA 17-651 (Amendment)
Heparin Sodium Injection, U.S.P.
(Derived from Porcine Intestinal Mucosa)
Volume 2, Amendment IV

Dear Dr. Temple,

By means of a telephone communication on July 18 from Mr. Robert Walters, we were requested to provide the following information toward the approval of our Abbreviated New Drug Application for the above-mentioned pharmaceutical preparation:

1. Letter from ——— authorizing the Food and Drug Administration to access their Drug Master File. Accordingly, we are enclosing copies of letters we sent on December 6, 1976 to the FDA providing such authorization.

2. A letter describing the relationship between ——— and ———. We requested ——— to send a letter to your attention regarding this matter, a copy is attached.

3. As requested by Mr. Robert Walters, we will delete ——— from our labeling at the next printing.

At this time, we request to withdraw the full list of the articles used as components of the drug (page 25 of our original submission) and replace it with the attached listing. We are doing this because there was an incorrect reference to use of ——— which is used in preparation of another product and we are including an alternate supplier of stoppers ———. The pertinent data regarding the ——stopper is also included in this submission.

RECEIVED
AUG 3 19[redacted]
HFD-110
BUREAU OF DRUGS

Sterile Pharmaceutical Products

We are also submitting at this time for your consideration and approval fill volume protocol providing for excess fill volumes for each of our heparin products.

We trust that this material completes our requirements regarding the approval of our Abbreviated New Drug Application for Heparin Sodium Injection, U.S.P. (Derived from Porcine Intestinal Mucosa).

Sincerely yours,

LYPHO-MED, INCORPORATED

Michael Hanushewsky
Director of Regulatory Affairs

Encl.

MH/rz

NDA 17-651

AUG 0 1977

Lypho-Med, Inc.
4020 West Division Street
Chicago, Illinois 60651

Gentlemen:

We acknowledge receipt of your resubmitted application for the following:

Name of Drug: Heparin Sodium Injection, U.S.P.
(Derived from Porcine Intestinal Mucosa)

NDA Number: 17-651

Date of Resubmitted Application: August 3, 1977

Date of Receipt: August 3, 1977

All communications concerning this NDA should be addressed as follows:

Bureau of Drugs HFD-110
Attention: DOCUMENT CONTROL ROOM 16B-30
5600 Fishers Lane
Rockville, Maryland 20852

Sincerely yours,

TWD 8/8/77

Thomas H. Davis
Supervisory Consumer Safety Officer
Division of Cardio-Renal
Drug Products
Bureau of Drugs

cc: CHI-DO
NDA Orig.
HFD-110
HFD-110/SCSO
HFD-110/APSmith/8/4/77/wh/8/5/77

RESUBMITTED APPLICATION
ACKNOWLEDGEMENT

Lypho-Med, Inc.

a subsidiary of Stone container corporation

FDA. est. no. 14-17023

4020 west Division street
Chicago, Illinois 60651

312. 342-6170

PERSONNEL SUBMITTED
Michael Hanushewsky

December 6, 1977

Robert J. Temple, M.D., Director
Cardiorenal Division
Office of Scientific Evaluation
BUREAU OF DRUGS
5600 Fishers Lane
Rockville, Maryland 20852

AF
Permit the FPL. As in compliance with DESI 552 Notice (10/7/77).
AAS/12/13/77

RE: NDA 17-651 (Amendment)
Heparin Sodium Injection, U.S.P.
(Derived from Porcine Intestinal Mucosa)
Volume 2, Amendment V

Dear Dr. Temple,

As requested by Dr. R. Wolters and Mr. A. Auer, we are submitting our final labeling for the above-mentioned product.

Please note that the enclosed package inserts are in the final form and conform to the requirements set forth in the October 7, 1977 Federal Register Notice (42: 54623-6).

Also, we request at this time to withdraw _____ as an outside testing laboratory for Heparin Sodium powders and injection. Henceforth, we will send these materials for potency testing to _____

We trust that the attached materials and information completes our requirements regarding the approval of our New Drug Application for Heparin Sodium Injection, U.S.P. (Derived from Porcine Intestinal Mucosa).

Sincerely yours,

LYPHO-MED, INCORPORATED

Michael Hanushewsky
Director of Regulatory Affairs

MH/rz

RECEIVED
DEC 6 1977
HFD-110
BUREAU OF DRUGS

ACTION:
REVIEWER:
DATE:

Sterile Pharmaceutical Products
Custom & Bulk Lyophilization