

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***  
**ANDA 63-014**

**Name:** Penicillin G Sodium for Injection, USP

**Sponsor:** Marsam Pharmaceuticals, Inc.

**Approval Date:** September 13, 1988

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**ANDA 63-014**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**ANDA 63-014**

**APPROVAL LETTER**

SEP 13 1988

Our Reference: 63-014

Marsam Pharmaceuticals, Inc.  
Attention: Howard C. Zell, Ph.D.  
Building 31, Olney Avenue  
P.O. Box 1022  
Cherry Hill, N.J. 08034

Dear Dr. Zell:

Reference is made to your Abbreviated Antibiotic Drug Application for Penicillin G Sodium for Injection, U.S.P.

Please also refer to your additional submission dated September 2, 1988.

We have completed our review of the application and it is approved.

An expiration date of twenty-four (24) months should be used on each batch of the drug to be manufactured and packaged as described in the application.

Place drug samples from the first three production batches into your stability program and test each batch at three (3) month intervals during the first year of aging, at six (6) month intervals during the second year, annually thereafter. As the data become available they should be furnished to this office at six (6) month intervals throughout the authorized shelf life of the subject drug.

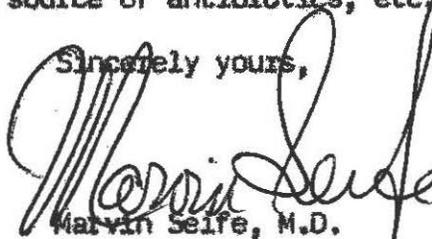
For Initial Campaigns: We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final printed. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Advertising and Labeling (HFD-240). Also, please do not use Form FD-2253 for this submission.

For Subsequent Campaigns: We call your attention to regulation 21 CFR 314.81(b)(3) which requires that all material for any subsequent advertising or promotional campaigns at the time of their initial use be submitted to our Division of Drug Advertising and Labeling (HFD-240) with a completed Form 2253. A copy of Form FD-2253 is enclosed for your convenience.

Please be reminded that since you are manufacturing the subject drug for the first time, that 21 CFR 314.81 requires that certain records and reports be submitted following approval of the application.

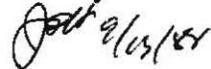
The application should be kept up to date by submitting supplements whenever changes are contemplated in the manufacturing and/or laboratory procedures, controls, packaging, labeling, source of antibiotics, etc.

Sincerely yours,

 9/13/88

Marvin Seife, M.D.  
Director  
Division of Generic Drugs  
Office of Drug Standards  
Center for Drugs and Biologics

HFD-235  
HFD-235/OD  
HFD-83  
R/D JSinger  
R/D init JHarrison  
HFD-230/Dr. Seife  
9-11-88 bcw 5084d

 9/13/88  
 9/13/88

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**ANDA 63-014**

**LABELING**

Prepared: \_\_\_\_\_ u/ml  
 Concentration: \_\_\_\_\_ u/ml

**PREPARATION OF SOLUTION**  
 Add 22 mL, 16 mL, 8 mL, or 3 mL diluent to provide  
 250,000 u, 250,000 u, 500,000 u, or 1,000,000 u per mL,  
 respectively.  
 Storage instructions may be found in refrigerator 1 week without  
 significant loss of potency.  
 Stability: For Intramuscular or Intravenous drip use

**SQUIBB | Marsam**  
 NDC 0003-0668-05

**5,000,000 units  
 PENICILLIN G SODIUM  
 for INJECTION USP**

Usual dosage: See insert  
 Caution: Federal law prohibits  
 dispensing without prescription

Vial provides 5,000,000 units penicillin G sodium with  
 approx. 140 mg sodium bicarbonate. Each 5 mL contains  
 approx. 100 million units penicillin G sodium. One  
 million units penicillin G sodium is approx. 2.0 mg  
 sodium.  
 Store at room temperature prior to constitution  
 © 1988 Hoechst-Roussel, Inc.  
 Made in the U.S.A.  
 For information contact:  
 SQUIBB-MARSAM, INC.  
 Kewanee, Illinois 60141  
 or Marsam Pharmaceuticals Inc.  
 Cherry Hill, NJ 08002 C2379 J 68805

Prepared: \_\_\_\_\_ u/ml  
 Concentration: \_\_\_\_\_ u/ml

**PREPARATION OF SOLUTION**  
 Add 22 mL, 16 mL, 8 mL, or 3 mL diluent to provide  
 250,000 u, 250,000 u, 500,000 u, or 1,000,000 u per mL,  
 respectively.  
 Storage instructions may be found in refrigerator 1 week without  
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 Kewanee, Illinois 60141  
 or Marsam Pharmaceuticals Inc.  
 Cherry Hill, NJ 08002 C2379 J 68805

**SQUIBB® Marsam®**

1 box • 10 vials

NDC 0003-0668-05

**5,000,000 units per vial**  
**PENICILLIN G SODIUM**  
for INJECTION USP

Caution: Federal law prohibits  
dispensing without prescription

**PENICILLIN G SODIUM for INJECTION USP**

Each vial provides 5,000,000 units penicillin G sodium with approx. 140 mg citrate buffer (composed of sodium citrate and not more than 4.6 mg citric acid). One million units penicillin contains approx. 2.0 mEq sodium.

**Sterile • For intramuscular or intravenous drip use**

Usual dosage: See insert

**PREPARATION OF SOLUTION:** Add 23 mL, 18 mL, 8 mL, or 3 mL diluent to provide 200,000 u, 250,000 u, 500,000 u, or 1,000,000 u per mL, respectively.

Sterile solution may be kept in refrigerator 1 week without significant loss of potency.

**Store at room temperature prior to constitution**

© 1986 Squibb-Marsam, Inc.

Mfd. for Squibb-Marsam, Inc., Cherry Hill, NJ 08034

by Marsam Pharmaceuticals Inc.

Cherry Hill, NJ 08034

C5347 / 66805

**SQUIBB® Marsam®**

1 box • 10 vials

NDC 0003-0668-05

**5,000,000 units per vial**  
**PENICILLIN G SODIUM**  
for INJECTION USP

Caution: Federal law prohibits  
dispensing without prescription

**PENICILLIN G SODIUM for INJECTION USP**

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**PREPARATION OF SOLUTION:** Add 23 mL, 18 mL, 8 mL, or 3 mL diluent to provide 200,000 u, 250,000 u, 500,000 u, or 1,000,000 u per mL, respectively.

Sterile solution may be kept in refrigerator 1 week without significant loss of potency.

**Store at room temperature prior to constitution**

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by Marsam Pharmaceuticals Inc.

Cherry Hill, NJ 08034

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**SQUIBB® Marsam®**

1 box • 10 vials

NDC 0003-0668-05

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Usual dosage: See insert

**PREPARATION OF SOLUTION:** Add 23 mL, 18 mL, 8 mL, or 3 mL diluent to provide 200,000 u, 250,000 u, 500,000 u, or 1,000,000 u per mL, respectively.

Sterile solution may be kept in refrigerator 1 week without significant loss of potency.

**Store at room temperature prior to constitution**

© 1986 Squibb-Marsam, Inc.

Mfd. for Squibb-Marsam, Inc., Cherry Hill, NJ 08034

by Marsam Pharmaceuticals Inc.

Cherry Hill, NJ 08034

C5347 / 66805

**CAUTION: Federal law prohibits dispensing without prescription.**



## PENICILLIN G SODIUM FOR INJECTION USP

### DESCRIPTION

Penicillin G Sodium for Injection is crystalline penicillin G sodium as a sterile powder. The preparation contains approximately 28 mg citrate buffer (composed of sodium citrate and not more than 0.92 mg citric acid) and 2.0 mEq sodium per million units of penicillin.

### CLINICAL PHARMACOLOGY

Penicillin G is bactericidal against penicillin-susceptible microorganisms during the stage of active multiplication. It acts by inhibiting biosynthesis of cell-wall mucopeptide. It is not active against the penicillinase-producing bacteria, which include many strains of staphylococci. Penicillin G is highly active *in vitro* against staphylococci (except penicillinase-producing strains), streptococci (groups A, C, G, H, L, and M) and pneumococci. Other organisms susceptible *in vitro* to penicillin G are *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae*, *Bacillus anthracis*, Clostridia, *Actinomyces bovis*, *Streptobacillus moniliformis*, *Listeria monocytogenes*, and Leptospira; *Treponema pallidum* is extremely susceptible. Some species of gram-negative bacilli are susceptible to moderate to high concentrations of penicillin G obtained with intravenous administration. These include most strains of *Escherichia coli*; all strains of *Proteus mirabilis*, Salmonella, and Shigella; and some strains of *Enterobacter aerogenes* (formerly *Aerobacter aerogenes*) and *Alcaligenes faecalis*.

Susceptibility plate testing: If the Kirby-Bauer method of disc susceptibility is used, a 10 u penicillin disc should give a zone greater than 28 mm when tested against a penicillin-susceptible bacterial strain.

Aqueous penicillin G is rapidly absorbed following both intramuscular and subcutaneous injection. Approximately 60 percent of the total dose of 300,000 u is excreted in the urine within this five-hour period. Therefore, high and frequent doses are required to maintain the elevated serum levels desirable in treating certain severe infections in individuals with normal kidney function. In neonates and young infants and in individuals with impaired kidney function, excretion is considerably delayed.

### INDICATIONS AND USAGE

Penicillin G Sodium for Injection is indicated in the treatment of severe infections caused by penicillin G-susceptible microorganisms when rapid and high penicillinemia is required. Therapy should be guided by bacteriological studies, including susceptibility tests, and by clinical response.

The following infections will usually respond to adequate dosage:

**Streptococcal Infections.** Note: streptococci in groups A, C, G, H, L, and M are very susceptible to penicillin G. Some group D organisms are susceptible to the high serum levels obtained with aqueous penicillin G. Aqueous penicillin G sodium is the penicillin dosage form of

choice for bacteremia, empyema, severe pneumonia, pericarditis, endocarditis, meningitis, and other severe infections caused by susceptible strains of the gram-positive species listed above.

**Pneumococcal infections; Staphylococcal infections**—penicillin G-susceptible; **Anthrax; Actinomycosis; Clostridial infections** (including tetanus); **Diphtheria** (to prevent the carrier state); **Erysipeloid endocarditis** (*Erysipelothrix insidiosa*); **Vincent's gingivitis and pharyngitis** (fusospirochetosis)—Severe infections of the oropharynx (Note: necessary dental care should be accomplished in infections involving gum tissue.) and **lower respiratory tract and genital area infections** due to *F. fusiformis* spirochetes; **Gram-negative bacillary infections** (bacteremias)—(*E. coli*, *E. aerogenes*, *A. faecalis*, *Salmonella*, *Shigella* and *P. mirabilis*); **Listeria infections** (*L. monocytogenes*); **Meningitis and endocarditis; Pasteurella infections** (*P. multocida*); **Bacteremia and meningitis; Rat-bite fever** (*S. minus* or *S. moniliformis*); **Gonorrheal endocarditis and arthritis** (*N. gonorrhoeae*); **Syphilis** (*T. pallidum*) including congenital syphilis; **Meningococcal meningitis**.

**Prevention of bacterial endocarditis (Patients unable to take oral antibiotics)**—Although no controlled clinical efficacy studies have been conducted, aqueous crystalline penicillin G for injection (except penicillin G procaine suspension) has been suggested by the American Heart Association and the American Dental Association for prophylaxis against bacterial endocarditis in patients with congenital heart disease or rheumatic or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the upper respiratory tract.<sup>1</sup> Since it may happen that *alpha* hemolytic streptococci relatively resistant to penicillin may be found when patients are receiving continuous oral penicillin for secondary prevention of rheumatic fever, prophylactic agents other than penicillin may be chosen for these patients and prescribed in addition to their continuous rheumatic fever prophylactic regimen. **NOTE: When selecting antibiotics for the prevention of bacterial endocarditis the physician or dentist should read the full**

**Joint statement of the American Heart Association and the American Dental Association.<sup>1</sup>**

#### CONTRAINDICATIONS

Contraindicated in patients with a history of hypersensitivity to any penicillin.

#### WARNINGS

Serious and occasional fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral administration, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with cephalosporins. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids. Serious anaphylactoid reactions are not controlled by antihistamines alone, and require such emergency measures as the immediate use of epinephrine, aminophylline, oxygen, and intravenous corticosteroids.

#### PRECAUTIONS

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

In prolonged therapy with penicillin and particularly with high dosage schedules, periodic evaluation of the renal and hematopoietic systems is recommended.

In streptococcal infections, therapy must be sufficient to eliminate the organism (10 days minimum); otherwise the sequelae of streptococcal disease may occur. Cultures should be taken following the completion of

treatment to determine whether streptococci have been eradicated.

In high doses (above 10 million u), intravenous aqueous penicillin G sodium should be administered slowly because of the adverse effects of electrolyte imbalance from the sodium content of the penicillin. The patient's renal, cardiac and vascular status should be evaluated and if impairment of function is suspected or known to exist, a reduction in the total dosage should be considered. Frequent evaluation of electrolyte balance, and renal and hematopoietic function is recommended during therapy when high doses of intravenous aqueous penicillin G sodium are used.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms, including fungi. Should superinfection occur, appropriate measures should be taken. Indwelling intravenous catheters encourage superinfections and should be avoided whenever possible.

Therapy of susceptible infections should be accompanied by any indicated surgical procedures. In suspected staphylococcal infections, proper laboratory studies, including susceptibility tests, should be performed.

When treating gonococcal infections in which primary or secondary syphilis may be suspected, proper diagnostic procedures, including darkfield examinations, should be done. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months. All cases of penicillin-treated syphilis should receive clinical and serological examinations every six months for at least two or three years.

Any entry into the container to effect solution of the powder or withdrawal of contents must be accomplished with strict aseptic technique and sterile equipment.

#### ADVERSE REACTIONS

Penicillin is a substance of low toxicity but does possess a significant index of sensitization.

The hypersensitivity reactions reported are skin rashes ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; and serum sickness-like reactions including chills, fever, edema, arthralgia, and prostration. Severe and occasionally fatal anaphylaxis has occurred (see WARNINGS).

Hemolytic anemia, leukopenia, thrombocytopenia, neuropathy, and nephropathy are rarely observed adverse reactions and are usually associated with high intravenous dosage. Urticaria, other skin rashes, and serum sickness-like reactions may be controlled by antihistamines and, if necessary, corticosteroids. Whenever such reactions occur, penicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to penicillin therapy. High dosage of penicillin G sodium may result in congestive heart failure due to high sodium intake.

The Jarisch-Herxheimer reaction has been reported in patients treated for syphilis.

#### DOSAGE AND ADMINISTRATION

Penicillin G Sodium for Injection may be given intramuscularly or by continuous intravenous drip.

The usual dosage recommendation is as follows:

**Severe infections due to susceptible strains of streptococci, pneumococci, and staphylococci; bacteremia, pneumonia, endocarditis, pericarditis, empyema, meningitis and other severe infections:** a minimum of 5 million u daily.

**Anthrax:** a minimum of 5 million u/day in divided doses until cure is effected; **Actinomycosis:** 1 to 6 million u/day for cervicofacial cases; 10 to 20 million u/day for thoracic and abdominal disease; **Clostridial infections** (as adjunctive therapy to antitoxin): 20 million u/day; **Diphtheria—**adjunctive therapy to antitoxin for prevention of the carrier state: 300,000 to 400,000 u/day in divided doses for 10 to 12 days; **Erysipeloid: Endocarditis:** 2 to 20 million u/day for four to six weeks; **Fusospirochetal infections** (fusospirochetosis)—severe infections of the oropharynx, lower respiratory tract and genital area: 5 to 10 million u/day; **Gram-negative bacillary infections** (*E. coli*, *E. aerogenes*, *A. faecalis*, *Salmonella*, *Shigella*, and *P. mirabilis*); **Bacteremia:** 20 to 80 million u/day; **Listeria infections** (*L. monocytogenes*): **Neonates:** 500,000 to 1 million u/day; **Adults with meningitis:** 15 to 20 million u/day for two weeks; **Adults with endocarditis:** 15 to 20 million u/day for four weeks; **Pasteurella infections** (*P. multocida*): **Bacteremia and meningitis:** 4 to 6 million u/day for two weeks; **Rat-bite fever** (*S. minus* or *S. moniliformis*): 12 to 15 million u/day for three to four weeks.

**Gonorrheal endocarditis and arthritis:** a minimum of 5 million u daily.

**Syphilis—**aqueous penicillin G sodium may be used in the treatment of acquired and congenital syphilis but, because of the necessity of frequent dosage, hospitalization is recommended. Dosage and duration of therapy is determined by the age of the patient and the stage of the disease.

**Meningococcal meningitis:** 1 to 2 million u IM every two hours or continuous IV drip of 20 to 30 million u/day.

**Prevention of bacterial endocarditis (Patients unable to take oral antibiotics)—**For prophylaxis against bacterial endocarditis<sup>1</sup> in patients with congenital heart disease or rheumatic or other acquired valvular heart disease when undergoing dental procedures or surgical procedures of the upper respiratory tract, administer 2 million u (50,000 u/kg for children) aqueous penicillin G, **except** penicillin G procaine suspension, intravenously or intramuscularly 30 to 60 minutes before the procedure and 1 million u (25,000 u/kg for children) six hours later. Doses for children should not exceed recommendations for adults for a single dose or for a 24-hour period.

**Preparation of Solutions**

Solutions of penicillin should be prepared as follows: Loosen powder. Hold vial horizontally and rotate it while *slowly* directing the stream of diluent against the wall of the vial. Shake vial vigorously after all the diluent has been added. Depending on the route of administration, use Sterile Water for Injection USP, Isotonic Sodium Chloride Injection USP, or Dextrose Injection USP. NOTE: Penicillins are rapidly inactivated in the presence of carbohydrate solutions at alkaline pH.

Reconstitute with 23 mL, 18 mL, 8 mL, or 3 mL diluent to provide concentrations of 200,000 u, 250,000 u, 500,000 u, or 1,000,000 u per mL, respectively.

**HOW SUPPLIED**

Penicillin G Sodium for Injection USP is available in vials providing 5 million u of crystalline penicillin G sodium.

**Storage**

The dry powder is relatively stable and may be stored at room temperature without significant loss of potency. Sterile solutions may be kept in the refrigerator one week without significant loss of potency. Solutions prepared for intravenous infusion are stable at room temperature for at least 24 hours.

**REFERENCE**

1. American Heart Association: Prevention of bacterial endocarditis. Circulation 70: 1123A-1127A, 1984

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Manufactured for  
**SQUIBB-MARSAM, INC**  
Cherry Hill, NJ 08034  
by Marsam Pharmaceuticals Inc.  
Cherry Hill, NJ 08034

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 63-014**

**CHEMISTRY REVIEWS**

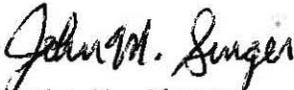
Manufacturing and Controls Review  
63-014

Penicillin G Sodium for Injection, U.S.P.  
Marsam Pharmaceuticals Inc.

Material Reviewed: A-002 dated September 2, 1988  
Exhibit Sample Testing Results dated August 30, 1988

1. Final Printed Labeling - satisfactory.
2. Exhibit Sample Testing Results - satisfactory. See memo from HFD-473 dated August 30, 1988.
3. Establishment Evaluation Request - satisfactory.

Recommendation - The application may be approved.

  
John M. Singer

Manufacturing and Controls Review  
63-014

Penicillin G Sodium for Injection, U.S.P.  
Marsam Pharmaceuticals Inc.

Material Reviewed: A-001 dated June 23, 1988  
A-002 dated July 8, 1988

Applicant's submissions respond to our not approvable letter dated June 29, 1988.

1. Stability Data - satisfactory.

The applicant has submitted room temperature and accelerated stability data from three batches of drug product (#8803007, #8803008 and #8803009) stored in the market container/closure system for three months. Assays are satisfactory.

Expiration Dating Period - 24 months.

2. Explanation for the following filling operation terms: (b) (4)  
(b) (4) satisfactory.

3. Precautions to insure sterility (b) (4)  
operations - satisfactory.

4. Final Printed Labeling - to be submitted at a later date.

Recommendation - the application remains not approvable due to #4.

*John M. Singer*  
John M. Singer

Manufacturing and Control Review

Abbreviated Antibiotic Drug Application #63-014

Date of Application: May 24, 1988

Date of Receipt: May 27, 1988

Applicant: Marsam Pharmaceuticals, Inc.  
Building 31  
Olney Ave.  
P.O. Box 1022  
Cherry Hill, N.J. 08034

Product: Penicillin G Sodium for Injection

Product is eligible for marketing when it meets the specifications prescribed by 21 CFR 440.281b.

1/2 Components/Composition:

Sterile Penicillin G Sodium, U.S.P.	<u>UNITS PER VIAL</u> 5,000,000
-------------------------------------	------------------------------------

(b) (4)

Applicant obtains Sterile Penicillin G Sodium, U.S.P. (b) (4) from the following FDA approved sources:

- 1) (b) (4)
- 2) (b) (4)

3. Manufacturing process:

A. Manufacturing facility location

Marsam Pharmaceuticals Inc.  
Building 31  
Olney Ave.  
P.O. Box 1022  
Cherry Hill, N.J. 08034

B. Raw material controls - satisfactory. The applicant performs adequate testing of the (b) (4) active ingredient. It meets the specifications listed in 21 CFR 440.1081a.

C. Description of facility and equipment - Satisfactory.

- D. Personnel - Satisfactory.
- E. Description of Batch numbering system - Satisfactory.
- F. Filling Instructions - satisfactory.  
Description of filling equipment - satisfactory.
- G. Master formula record - satisfactory.

5 mm units/50 mL (b) (4) (b) (4) vials

- H. Batch records - satisfactory.

The applicant has submitted the following batch records:

#8803007	(b) (4)	(b) (4) vials
#8803008	(b) (4)	vials
#8803009	(b) (4)	vials

- I. Sterility Control - Unsatisfactory. The applicant did not contain precautions to insure the sterility of the drug product (b) (4) (b) (4) Other controls are satisfactory.

4. Quality Control:

- A. Analytical Procedures - satisfactory.
- B. Standards for acceptance of each lot of the finished drug - satisfactory.

The standards are the same as those listed in 21 CFR 440.281b and the USP.

- C. Container/closure system - satisfactory.

The applicant proposes to use 50 mL Type II fling vials. They are manufactured by (b) (4). The stopper is a 20 mm (b) (4) gray stopper manufactured by the (b) (4). The vial seal is made of aluminum with a flip-off button. It is manufactured by (b) (4).

Container Closure controls - satisfactory.

- D. Stability testing protocol - satisfactory  
Stability commitment - satisfactory.  
Stability data - Unsatisfactory.

The applicant has submitted room temperature and accelerated stability data from three batches of drug product (lots #8803007, #8803008 and #8803009) stored in the 50 mL container/closure system for one month.

Review is deferred pending receipt of three month data.

Reconstitution study data - satisfactory.

- E. Expiration Dating Period - Applicant requests 24 months. We cannot set an expiration dating period due to the lack of and data.
- F. Labeling - satisfactory. The applicant has revised approved labeling from #60-363.
- G. The drug product is Rx.
- H. Bioavailability - not required since the drug product is administered IM or IV.
- I. Consulting laboratory: (b) (4)
- J. Exhibit Samples - sent to FDA laboratory on June 8, 1988.

Recommendation - the application is not approvable at this time due to the following deficiencies:

1. The application did not contain room temperature and accelerated stability data from three batches of drug product stored in the container/closure system for three months (assays at 0, 1, 2 and 3 months).
2. The application did not adequately explain the following terms under (b) (4)
3. The application did not contain a description of the precautions to insure the sterility of the drug product (b) (4) (b) (4) operations.

*John M. Singer*  
John M. Singer

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 63-014**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

SEP 13 1988

NOTICE OF APPROVAL  
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER

63-014

DATE APPROVAL LETTER ISSUED

TO:

Press Relations Staff (HFI-40)

FROM:

Bureau of Drugs

Bureau of Veterinary Medicine

ATTENTION

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

TYPE OF APPLICATION

ORIGINAL NDA

SUPPLEMENT TO NDA

ABBREVIATED ORIGINAL NDA

SUPPLEMENT TO ANDA

CATEGORY

HUMAN

VETERINARY

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

Penicillin G Sodium

DOSAGE FORM

for Injection

HOW DISPENSED

RX

OTC

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

penicillin G sodium

per vial  
5,000,000 units

NAME OF APPLICANT (Include City and State)

Marsam Pharmaceuticals Inc.  
Building 31, Olney Ave.  
P.O. Box 1022  
Cherry Hill, N.J. 08034

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

antibiotic

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME

John M. Singer

DATE

9/9/88

FORM APPROVED BY

NAME

Marvin Seife, M.D.

DATE

9/13/88



# Memorandum

Date August 30, 1988

From Chief, Antimicrobial Drugs Branch  
HFD-473

Subject Forms 62-991 and 63-014; Penicillin G Potassium and Penicillin G Sodium for Injection, USP; Marsam Pharmaceuticals Inc.

To John M. Singer  
HFD-235

These two applications are reported jointly here because of the many common elements within them: the products differ only in the metal ion form and the variety of dosage levels.

These applications adequately describe the composition of these products. The raw materials for each are obtained from FDA approved sources as

(b) (4)

Adequate raw materials controls appear to be operative. The manufacturing process is essentially the (b) (4)

(b) (4)

(b) (4) penicillin.

The compendial testing of the finished product and (b) (4) material is all performed by in-house Marsam personnel except for the pyrogens tests. There are no (b) (4) of the finished product.

The batch numbers for commercial batches of these products are seven digit numbers in which: (b) (4)

(b) (4) A letter and a hyphenated digit suffix are used as required to indicate separate (b) (4) respectively. The exhibit samples have batch numbers of this type. Products that carry the Squibb-Marsam labeling encode the same information alphanumerically.

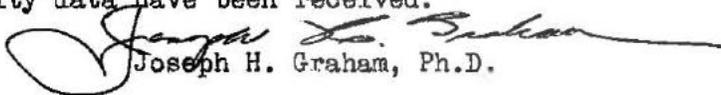
Adequate protocols for accelerated (37-40°C/75% RH) and long term (RT) stability studies are described. Summaries of test results up through one month's storage under both conditions in the market packages were submitted for three batches of each product. These data are insufficient to justify the 24 month expiry period requested for these products. Presumably, additional data have been submitted to you.

ADB received exhibit samples from the same batches used in the stability studies. All of these batches were manufactured in February and March 1988 and were therefore about 5-6 months old at the time of ADB's tests and assays. Each batch of the Pen G K product was manufactured from a (b) (4) batches 8803007 and 8803008 of the Pen G Na product were made from (b) (4)

(b) (4) The manufacture of each of these batches was completed on separate

days. There was no indication of maximum batch sizes, but since no (b)(4) is involved, ADB is not greatly concerned over their size since the most likely manufacturing (b)(4) (b)(4) batches. The samples were examined for conformance to USP XXI and CFR physicochemical specifications. All of the test results are satisfactory and the individual assay values are in close agreement. All except one of ADB's averaged potency values are lower than Marsam's and lower than the claimed (b)(4) formulation. These data are tabulated in the attached Chemistry Review Notes.

ADB finds these application to be incomplete on account of their insufficient stability data. These applications are satisfactory otherwise and ADB would concur in their approval provided that satisfactory additional stability data have been received.

  
Joseph H. Graham, Ph.D.

cc: HFD-470 (Overpeck)  
HFD-473 (Chem. Sec.; R/F)  
HFD-333 (Geissel)

JHG/ymb  
0208Y

Chemistry Review Notes  
August 22, 1988

RE: Form 62-991  
Penicillin G Potassium for Injection, USP  
Submitted by Marsam Pharmaceuticals Inc.

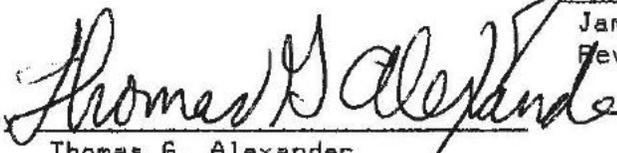
This applicant requests approval to market its generic penicillin G potassium for injection, USP in 4 different configurations (1,000,000 units/20ml vial, 5,000,000 units/50ml vial, 10,000,000 units/50ml vial, & 20,000,000 units/100ml vial).

The active ingredient, penicillin G potassium for injection, as raw material comes from (b) (4)

Raw materials, check tests on raw materials, manufacturing process, release tests on finished products, and stability study programs are adequately described. Stability data on exhibit samples are submitted. An expiry date of 24 months is proposed.

Three exhibit samples (M10580-M10582) submitted were tested and found to be within the limits specified in 21 CFR 440.280b & USP XXI. Test data from the company and FDA laboratories are tabulated in Table I.

Number of tests = 27  
Time spent = 20 hours

Reviewed by   
Thomas G. Alexander  
Chief, Chemistry Section

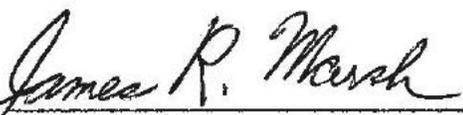
  
James R. Marsh  
Review Chemist

Table I: Test Data on Penicillin G Potassium for Injection, USP  
(Form 62-991)

Lot #	8802001		8802002		8802008	
M #	M10580		M10581		M10582	
Label claim (units)	1,000,000		5,000,000		20,000,000	
Vial size (ml)	20		50		100	
Laboratory	Co.	FDA	Co.	FDA	Co.	FDA
Moisture (LOD)		(b) (4)		(b) (4)		(b) (4)
NMT 1.5%						
Average	0.6	0.12	0.1	0.13	0.6	0.059
pH						
5.0 - 8.5	7.0	7.1	6.9	7.1	6.9	7.1
Identity (TLC)	pass	pass	pass	pass	pass	pass
Potency (iodom)		(b) (4)		(b) (4)		(b) (4)
90-120% LC						
Avg. % LC	100.7	101.1	103.8	102.5	106.1	101.5

Chemistry Review Notes  
August 22, 1988

RE: Form 63-014  
Penicillin G Sodium for Injection, USP  
Submitted by Marsam Pharmaceuticals Inc.

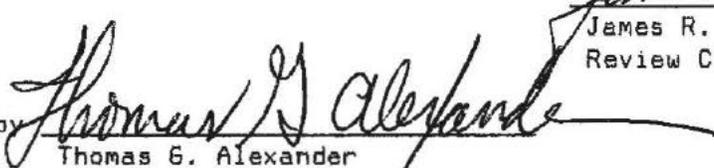
This applicant requests approval to market its generic penicillin G sodium for injection, USP in one configuration (5,000,000 units/50ml vial).

The active ingredient, penicillin G sodium for injection, as raw material comes from (b) (4)

Raw materials, check tests on raw materials, manufacturing process, release tests on finished products, and stability study programs are adequately described. Stability data on exhibit samples are submitted. An expiry date of 24 months is proposed.

Three exhibit samples (M10637-M10639) submitted were tested and found to be within the limits specified in 21 CFR 440.281b & USP XXI. Test data from the company and FDA laboratories are tabulated in Table I.

Number of tests = 27  
Time spent = 19 hours

Reviewed by   
Thomas G. Alexander  
Chief, Chemistry Section

  
James R. Marsh  
Review Chemist

Table I: Test Data on Penicillin G Sodium for Injection, USP  
(Form 63-014)

Lot #	8803007		8803008		8803009	
	M #	M10637	M #	M10638	M #	M10639
Laboratory	Co.	FDA	Co.	FDA	Co.	FDA
Moisture (LOD)		(b) (4)		(b) (4)		(b) (4)
NMT 1.5%						
Average	0.1	0.136	0.0	0.113	0.0	0.137
pH						
6.0 - 7.5	7.04	6.9	7.05	6.9	7.02	6.9
Identity (TLC)	pass	pass	pass	pass	pass	pass
Potency (iodom)		(b) (4)		(b) (4)		(b) (4)
90-120% LC						
Avg. % LC	111.2	101.9	113.6	101.5	106.5	102.9

Our Reference: 63-014

Marsam Pharmaceuticals, Inc.  
Attention: Judith U. Arnoff, R.Ph.  
Building 31, Olney Ave  
P.O. Box 1022  
Cherry Hill, N.J. 08034

July 15, 1988

Gentlemen:

Please refer to your Abbreviated Antibiotic Drug Application for Penicillin G Sodium for Injection, USP, and to your additional submissions dated June 23 and July 8, 1988.

We have completed our review of the submissions and conclude that the application remains not approvable since final printed labeling has not been submitted and exhibit sample testing has not been completed.

Please submit final printed labeling when available.

Sincerely yours,

John M. Singer  
Antibiotic Drug Review Branch  
Division of Generic Drugs

— HFD-235  
HFD-235/00  
R/D JSinger  
R/D init JHarrison  
HFD-230/Dr. Seife  
7-15-88 bcw 4807d

Our Reference: 63-014

JUN 29 1988

Marsam Pharmaceuticals, Inc.  
Attention: Judith U. Arnoff, R.Ph.  
Building 31, Olney Avenue  
P.O. Box 1022  
Cherry Hill, N.J. 08034

Gentlemen:

Please refer to your Abbreviated Antibiotic Drug Application dated May 24, 1988 for Sterile Penicillin G Sodium for Injection, U.S.P.

We have completed our review of the submission and conclude that the application is not approvable due to the following deficiencies:

1. The application did not contain room temperature and accelerated stability data from three batches of drug product stored in the container/closure system for three months (assays at 0, 1, 2 and 3 months).
2. The application did not adequately explain the following terms under (b) (4)  
(b) (4)
3. The application did not contain a description of the precautions to insure the sterility of the drug product (b) (4)  
(b) (4) operations.

Please submit 6 copies of final printed labeling that are identical in content and format to the draft labeling.

Sincerely yours,

John M. Singer  
Antibiotic Drug Review Branch  
Division of Generic Drugs

HFD-235  
HFD-235/00  
R/D JSinger  
R/D init JHarrison  
HFD-230/Dr. Seife  
6-27-88 bcw 4744d

June 8, 1988

Chemist, HFD-235

Abbreviated Antibiotic Drug Application 63-014

Director, Antimicrobial Drug Branch, HFD-473

Marsam Pharmaceuticals, Inc. has submitted an Abbreviated Antibiotic Drug Application for Penicillin G Sodium for Injection, U.S.P. Please perform the required compendial tests.

The following are being forwarded with this memo:

1. Duplicate copy of the applicant.
2. Samples with Certificates of Analysis for three batches.

If there are any questions, I may be reached at 443-4340.

John M. Singer

HFD-235  
HFD-235/OD  
R/D JSinger 6/8/88  
HFD-230/Dr. Seife  
6/8/88 bcw 4659d