

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**62483**

**CHEMISTRY REVIEW(S)**

Manufacturing and Controls Review  
#62-483

The submission dated January 12, 1984, responds to our letter dated January 4, 1984.

1. Stability Data - the submission contains data from two batches of product (13D001, 13E002) stored in the market container at 24°C, 37°C, and at 50°C for periods up to 90 days.

The results of testing are satisfactory, except, for the pH at 50°C for 90 days. This result (at very high temperature) should not delay the approval of this product.

Expiration Date - based on satisfactory stability data for two batches of product, an expiration date of 2 years is appropriate at this time.

2. Exhibit Samples - the firm submitted samples from two batches of product. This was sent to our laboratory on January 17, 1984.

On January 19, 1984, I discussed this product with Charles Ise, Ph.D. of the Division of Biopharmaceutics. He indicated that since the product was to be manufactured by another member of the Johnson & Johnson Corp., his division did not require bioavailability data.

Based on that discussion, and on the data submitted in the application, I feel that the product should be approved at this time.

*JMS*  
John M. Singer

HFN-535  
HFN-535/OD  
R/D JMSinger 1/19/84  
HFN-530 (Dr. Seife)  
ft mw 1/23/84 w4580c

Manufacturing and Controls Review  
#62-483

Date of Submission - December 8, 1983

Applicant has responded to our not approvable letter dated November 17, 1983.

1. Raw material testing/controls - satisfactory.
2. Filling operations - satisfactory.
3. Container/closure controls - satisfactory.
4. Standards for Acceptance of the finished drug product - satisfactory.
5. Stability Data - unsatisfactory.

The applicant states, "...we have incorporated by reference all of the stability data included in Form 5 #50-448..."

This is not acceptable. Ortho Pharmaceutical Corporation has not demonstrated to us that it can manufacture this product. Previously, Ortho was merely a distributor of the product. Now, they intend to manufacture the drug at a new facility, with new equipment and personnel.

Ortho must first prove to us that they are capable of manufacturing this product, as other firms must do. Stability data from three lots of product should be submitted for our review.

6. Exhibit Samples - unsatisfactory.

The applicant has submitted samples from only one batch (13D001) of product.

7. Labeling - satisfactory.
8. Advertising/Labeling - satisfactory.
9. Bioavailability - waiver granted.

Conclusion - the application is not approvable at this time due to inadequate stability data and inadequate exhibit samples.

*/S/*  
John M. Singer

HFN-535  
HFN-535/OD  
R/D JMSinger 12/29/83  
HFN-530/Dr. Seife

January 17, 1984

Chemist, HFN-535

Form 6 #62-483 - Grifulvin V (griseofulvin microsize) Suspension

Director, Anti-Microbial Drug Branch, HFN-416

Ortho Pharmaceutical Corp. has submitted a Form 6 application for Grifulvin V (griseofulvin microsize) Suspension. Please perform the required compendial tests (21 CFR 449.120 c).

The following are being forwarded with this memo:

1. triplicate copy of the application
2. samples from two batches of product.

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

John H. Singer

HFN-535  
HFN-535/OD  
R/D JHSinger 1/13/84  
HFN-530/Dr. Seife  
ft m: 1/17/84 4413c

**BEST POSSIBLE COPY**

January 17, 1984

Chemist, HFN-535

Antibiotic Form 6 #62-483 - Grifulvin V (griseofulvin microsize) Suspension, 125 mg/ml by Ortho Pharmaceutical Corp.

Charles Ise, HFN-522

McNeil Laboratories holds an approved Antibiotic Form 5 application for Grifulvin V (griseofulvin microsize) Suspension, 125 mg/ml. Ortho Pharmaceutical Corp. is listed as a distributor of the product.

Ortho Pharmaceutical Corp. now intends to take over production of this product from McNeil Laboratories (both companies are subsidiaries of Johnson & Johnson). Ortho will use the same formulation and equipment as used by McNeil, but will manufacture the product at a new facility with Ortho personnel.

Ortho Pharmaceutical Corp. has requested a waiver of the bioavailability requirement. Please comment.

John M. Singer

HFN-535  
HFN-535/OD  
R/D JMSinger 1/13/84  
HFN-530/Dr. Seife

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

Form approved:  
OMB No. 57-R0126

**IMPORTANT:** No batches of Antibiotic Drugs may be certified or released unless this form, Antibiotic Application, Form FD 1675, has been filed with the Food and Drug Administration (21 CFR, Parts 430 through 460).

APPLICABLE PROCEDURES	Check one	FOOD AND DRUG ADMINISTRATION USE ONLY	
Form 5 request under 431.17 to provide for certification of a new antibiotic or antibiotic-containing product.		DATE APPROVED 1/26/84	ACCOUNT NO. 1
Form 6 data to accompany or precede every initial request under 431.1 for certification of an antibiotic drug covered by existing Regulations, Section 21CFR 449.120c	X	SIGNED /S/	
Form 5 amendment, Regulation Section _____, if known.		✓ (For the Commissioner of Food and Drug Administration Food and Drug Administration Department of Health, Education, and Welfare)	
Form 6, Regulation Section _____			
NAME OF APPLICANT (Last, First, MI) Ortho Pharmaceutical Corporation		DATE OF APPLICATION SEP 28 1983	
ADDRESS (Number, Street, City, State, ZIP Code) Route 202 South -- Raritan, New Jersey 08869			
NAME OF DRUG GRIFULVIN V (griseofulvin microsize) Suspension			

Commissioner  
Food and Drug Administration  
Department of Health, Education, and Welfare  
Rockville, Maryland 20852

Attention: Certifiable Drug Review, Staff (HFD-535)

In accordance with regulations promulgated under Section 507 of the Federal Food, Drug, and Cosmetic Act, as amended, we hereby submit this application with respect to an antibiotic product.

Attached hereto, in triplicate (except for the information required under item 9 (a) through (f) which is submitted in single copy) and constituting a part of this application are the following:

1. A full list of the articles used as components of the drug. This list should include all substances used in the fermentation, synthesis, extraction, purification or other method of preparation of any antibiotic and in the preparation of the finished dosage form, regardless of whether they undergo any change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

2. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed, as for example, amount per tablet or per millimeter, and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

3. A complete description of the methods and processes used in manufacturing, packing and labeling of the drug to preserve its identity, strength, quality, and purity in conformity with good manufacturing practices including:

- (a) Name and location of each plant conducting the operations.
- (b) Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.
- (c) Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material used in the fermentation, synthesis, extraction, and purification of the drug and for each ingredient used in the manufacture of the drug that is to be dispensed.
- (d) If it is a drug produced by fermentation:
  - (i) Source and type of microorganism used to produce the drug.
  - (ii) Composition of media used to produce the drug.
  - (iii) Type of precursor used, if any, to guide or enhance production of the antibiotic during fermentation.
  - (iv) Name and composition of preservative, if any, used in the broth.
  - (v) A complete description of the extraction and purification processes including the names and compositions of the solvents, precipitants, ion exchange resins, demulsifiers, and all other agents used.
  - (vi) If the drug is produced by a catalytic hydrogenation process, (such as tetracycline from chlortetracycline) a complete description of the process, including the name of the catalyst used, how it is removed, and how the drug is extracted and purified.

(e) If it is a drug that is synthesized by chemical processes, a detailed description of each chemical reaction with graphic formulas used to produce the drug, including the names and amounts of all substances used in the process.

(NOTE: If the applicant is not the manufacturer of the antibiotic used in making the drug, in lieu of the information required in 3(a) through 3(e), he should include the name and address of the manufacturer.)

(f) Method of preparation of the master formula records and individual batch records and manner in which these records are used.

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

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

(i) At what point in the process the drug is mixed homogeneously and a description of the equipment used for this purpose and its total capacity in terms of pounds, kilograms, gallons, or liters of the drug and the maximum quantity of the drug that is mixed in such equipment.

(j) A description, where applicable, of all equipment used in the fermentation, synthesis, extraction, purification, filtration, sterilizing, grinding, blending, mixing, tableting, encapsulating, filling, packaging, and labeling of the drug.

(k) If it is a sterile drug, a description of the methods used to insure the sterility of each batch and the controls used for maintaining its sterility, including a detailed description of the sterile areas where the drug is produced and packaged.

(l) Additional procedures employed which are designed to exclude contaminants (e.g., other drug substances, extraneous materials, etc.) and otherwise assure proper control of the product.

(m) Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug container to insure their suitability for the intended use.

(n) Controls used in the packaging and labeling of each batch to insure the standards of identity, strength, quality and purity of the drug.

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

(p) Precautions to insure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling, storage, and inventory control.

(q) Copies of all printed forms used by the applicant in the manufacture, packaging, and labeling of a batch.

(r) The name of each person responsible for each of the above operations and information concerning his scientific training and experience.

**4. A complete description of the tests and methods of assay and other controls used during the manufacture of the batch and after it is packaged.**

(a) Details of analytical procedures for all active ingredients. The analytical procedures should be capable of determining the active components and of assuring the identity of such components.

(b) Standards used for acceptance of each lot of the finished drug.

(c) A detailed description of the collection of the samples to be tested by the applicant and by the Food and Drug Administration.

(d) Copies of all printed forms used by the applicant in the laboratory control of raw ingredients and the finished batch.

(e) A complete description of the laboratory facilities used in controls, including:

(i) The location of the laboratory in relation to the plant where the drug is manufactured.

(ii) A description of the laboratory equipment available for performing tests and assays, and

(iii) The names of the persons who will be responsible for conducting the required laboratory tests and information concerning their scientific training and experience.

(f) If the applicant uses the services of a consulting laboratory, the name and address of such laboratory and a statement from such laboratory that includes the information required under 4(a), (b), and (e).

(g) An explanation of the exact significance of any batch numbers used in the manufacturing, processing, packaging, and labeling of the drug, including such control numbers that may appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

(h) A complete description of, and data derived from, stability studies of the potency and physical characteristics of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new antibiotic, for the finished dosage form of the drug in the container including a multiple-dose container in which it is to be marketed, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed.

(i) The expiration date needed to preserve the identity, strength, quality, and purity of the drug until it is used.

**5. The following samples shall be submitted with the application or as soon thereafter as they become available:**

(a) If it is a new antibiotic: 10 grams of the applicant's reference standard if an official standard has not been designated, plus 5 grams from each of three separate batches. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

(b) If it is a dosage form: 6 immediate containers (or 30 tablets or capsules) from each of three separate batches, except that if it is a sterile drug 30 containers shall be submitted from each of three batches.

(c) Include for samples submitted pursuant to items 5(a) or 5(b) detailed results of all laboratory tests made to determine the identity, strength, quality and purity of the batch represented by the sample.

(d) Additional samples shall be submitted on request.

(e) The requirements of items 5(a) or 5(b) may be waived in whole or in part on request of the applicant, or otherwise, when any such samples are not necessary.

**6. Each copy of the application shall contain a copy of each label and all other labeling to be used for the drug.**

(a) Each label, or other labeling, should be clearly identified or show its position on, or the manner in which it accompanies, the market package.

(b) The labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use, or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to laymen.

(c) If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purpose for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with 201.100 or 201.105.

(d) If no established name exists for a new antibiotic, the application shall propose a nonproprietary name for use as the established name for the substance.

(e) Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not be approved prior to the submission of the final printed label and labeling of the drug. No application may be approved if the labeling is false or misleading in any particular. *(If the article is a prescription drug, copies of proposed advertising may be submitted optionally for comment or approval).*

7. State whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

8. It is understood that the labeling, and advertising for the antibiotic drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will also contain substantially the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant hazards, contraindications, side effects, and precautions, contained in the labeling which is part of this application. It is understood that all representations in this application apply to the drug produced until an amendment providing for a change is approved by the Food and Drug Administration.

9. Full reports of investigations that have been made to show whether or not the drug is safe for use and efficacious in use.

If this is a Form 5 application submit one copy of (a) through (f) below

(a) An application may be found unsatisfactory unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the proposed labeling and includes all the following:

(i) Detailed reports of the preclinical investigations, including studies made on laboratory animals, in which the methods used and the results obtained are clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or premenopausal women.

(ii) Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations

made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

(iii) All information pertinent to an evaluation of the safety and efficacy of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application or pertinent information about any relevantly related drug. An adequate summary may be acceptable in lieu of a reprint of a published article which only supports other data submitted. Include any evaluation of the safety or efficacy of the drug that has been made by the applicant's medical department, expert committee, or consultants.

(iv) If the drug is a combination of previously investigated or marketed drugs an adequate summary of pre-existing information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

(b) An application may be found unsatisfactory unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the efficacy of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(c) The complete composition and/or method of manufacture of the drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 1, 2, 3 or 4 of the application in any way that would bias an evaluation of the report.

(d) An application shall include a complete list of the names and post office addresses of all investigators who received the drug.

(e) The information required by 9(a) through 9(d) may be incorporated in whole or in part by specific reference to information submitted under the provision of § 312.1.

(f) Explain any omission of reports from any investigator to whom the investigational drug has been made available. The unexplained omission of any reports of investigations made with the drug by the applicant, or submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, that would bias an evaluation of the safety of the drug or its efficacy in use constitutes grounds for finding the application unsatisfactory.

(g) If this is a Form 6 application, in lieu of the information required in 9(a) through 9(f) it should include data adequate to demonstrate that the drug is comparable to the drug for which certification has previously been provided.

10. If this is an amendment, full information on each proposed change concerning any statement made in the approved application. After an application is approved, an amendment may propose changes. An amendment should be submitted for any change beyond the variations

provided for in the approved application. An amendment may omit statements made in the approved application concerning which no change is proposed. Any mailing or promotional piece used after the drug is placed on the market is labeling requiring an amendment. An amendment should be submitted for proposed changes in labeling. If a change is made in the components, composition, manufacturing methods, facilities or controls, or in the labeling or advertising from the representations in an approved application and the drug is marketed before an amendment is approved for such change, certification of the drug may be suspended.

Very truly yours,

Ortho Pharmaceutical Corporation

(Applicant)

Per \_\_\_\_\_

A. J. Vazakas, Ph.D. *AJ Vazakas*

Manager of Regulatory Affairs

(Indicate Authority)

This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States. The data specified under the several numbered headings should be on separate sheets or sets of sheets, suitably identified. The sample of the drug, if sent under

separate cover, should be addressed to the attention of the National Center for Antibiotic Analysis and identified on the outside of the shipping package with the name of the applicant and the name of the drug as shown on the application. All applications and correspondence should be submitted in triplicate except for the information required under item 9(a) through (f) which should be submitted as a single copy attached to the original copy of the application.



62483

gms 4/2/84

Memorandum

Date March 28, 1984  
From Chief  
Antimicrobial Drugs Branch (HFN-416)  
Subject Form 62-483; Ortho Pharmaceutical Corporation; Griseofulvin (Micro size)  
Suspension  
To John M. Singer (HFN-535)

This abbreviated application covers the transfer of full manufacture, labeling and control of Grifulvin V, a previously approved drug, from McNeil Pharmaceutical Company to Ortho Pharmaceutical Corporation. With the exception of some differences in manufacturing equipment used by Ortho, the formulation and manufacturing process will be the same as that previously used by McNeil. The manufacturing process is described and most other routine control procedures are referenced to DMF

Two exhibit samples were submitted. ADB tested them for conformance to 21 CFR 449.120c. The attached laboratory report indicates that the samples are satisfactory.

This application is judged to be satisfactory from the analytical laboratory standpoint.

*/S/*  
Joseph H. Graham, Ph.D.

cc: HFN-410(Titus)  
HFN-416(Chem. Sec., R/F)  
HFN-333(Geissel)