CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 84-655

CORRESPONDENCE

NDA 83-009

AF 20-333

APR 24 1972

Rowell Laboratories, Inc.
Attention: Dr. Ben E. Greenwell
Baudette, Minnesota 56623

Gentlemen:

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

NAME of DRUG: Orasone - (Prednisone) Tablets

DATE of APPLICATION: April 14, 1972

DATE of RECEIPT: April 17, 1972

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

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

Sincerely yours,

Marvin Seife 4/21/72

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

cc:
MINN-DO
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/S/

Rec. WP Orig E

RESUBMISSION
NDA ORIG AMENDMENT

ROWELL LABORATORIES, INC.

BAUDETTE, MINNESOTA 56623 218/634-1866

BEN E. GREENWELL, Ph. D.
VICE PRESIDENT, RESEARCH

FPL

December 6, 1973

Marvin Seife, M.D.
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: NDA 83-009

Dear Doctor Seife:

In accordance with your letter of November 14, 1973, pertaining to our NDA 83-009 for ORASONE Tablets, 1 mg., 5 mg., 10 mg., and 20 mg., we hereby submit 12 copies each of the following final printed labels and labeling:

1. Labels for bottles of 100 of each tablet size.

2. Labels for bottles of 1000 of each tablet size.

3. Common package insert used for all four sizes of tablets.

We have on stability test at room temperature and ambient humidity samples from four typical production batches to monitor potency, friability, and dissolution characteristics at 12-month intervals throughout the expiration dating periods of the respective lots. As data are accumulated, these will be submitted along with our NDA Reports. If any lot on test is shown to be subpotent or to fail the U.S.P. dissolution rate test prior to the end of its expiration dating period, that lot will be withdrawn from the market and an investigation of our reserve samples of all other lots will be undertaken to determine the extent of the deficiency.

We trust that this completes all of the requirements for approval of NDA 83-009.

Yours truly,

ROWELL LABORATORIES, INC.

Ben E. Greenwell

Ben E. Greenwell, Ph.D.
Vice President, Scientific
and Regulatory Affairs

BEG:dat

Enc(s).

ORIG NEW CORRES

McMURRAY AND PENDERGAST
1815 H STREET, N. W.
WASHINGTON, D. C. 20006
AREA CODE 202 638-5550

RAYMOND D. McMURRAY
WILLIAM R. PENDERGAST
MARK E. BARMAK

CHARLES W. WHITMORE
VIRGINIA BAR
OF COUNSEL

99

November 20, 1972

ORIG

Marvin Seife, M.D.
Director
Division of Actions Implementation
DESI Project Office
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: NDA 83-009
ORASONE

Dear Doctor Seife:

We are counsel for Rowell Laboratories, Inc. and they have asked us to contact you with respect to a portion of your letter of November 8, 1972, regarding the above NDA. The portion they have asked us to contact you about relates to paragraph 1 on the first page of that letter and advises the company to withdraw the labels for the 10 and 20 mg. tablets. The company will respond to the rest of that letter.

In previous correspondence your office has indicated that an abbreviated NDA may not be obtained for a Prednisone tablet product containing 10 to 20 mgs. of Prednisone, since such potencies are not covered by DESI announcement 7750. It is Rowell Laboratories' position that the 10 and 20 mg. potencies are related to the drugs covered by DESI 7750, as the term "related" has been defined by FDA itself in the Federal Register of October 31, 1972 [37 F.R. 23185]. Additionally, it is the position of Rowell Laboratories that the 10 and 20 mg. potencies are, in fact, covered by the DESI announcement. That announcement recommends up to 60 mgs. Prednisone as an initial daily dose. Surely, 10 and 20 mg. potencies can be used to achieve this daily dosage. The NAS/NRC panel that reviewed Prednisone found that 60 mg. per day was an effective dose for indicated conditions and that is the dosage recommended for these potencies.

The whole purpose of the related drug regulation is to apply the findings in a DESI announcement to drugs which are not identical to the drugs evaluated in a DESI announcement. This application is to be made to drugs which are different but which are "related", as that term is defined in the regulation. Since it is the purpose of the related drug regulation to expand the scope of DESI announcements, we fail to see why that expansion does not also apply here. Is it the position of the FDA that, where a DESI announcement calls for an abbreviated new drug application, that DESI announcement is not applicable to related drugs?

Your prompt response to this inquiry will assist us in advising our client.

Very truly yours,

William R. Pendergast

WRP/bmd

Rev. w/f

RESUBMISSION
NDA ORIG AMENDMENT E

ROWELL LABORATORIES, INC.

BAUDETTE, MINNESOTA 56623 218/634-1866

ORIG

BEN E. GREENWELL, Ph. D.
VICE PRESIDENT, RESEARCH

November 21, 1972

Division of Actions Implementation
DESI Project Office
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20852

Ref: NDA 83-009; Your letter of November 8, 1972.

Gentlemen:

In reply to your letter of November 8, 1972, which listed additional deficiencies in our Abbreviated NDA 83-009, ORASONE Prednisone Tablets, I shall discuss the points in the order in which they appeared in your letter:

Regarding proposed labeling:

1. You requested that we withdraw the labels for 10 mg. and 20 mg. ORASONE tablets, but you did not reply to the questions raised in our letter of September 14, 1972, pertaining to the applicability of DESI 7750 to these dosage strengths. Our attorney, Mr. William R. Pendergast, 1815 H Street, N.W., Washington, D. C., is writing to you about this.

2. a) See 1., above.

b) We agree to put the PRECAUTIONS section where it belongs. This was inadvertently shifted in our Printing Department.

c) We agree to reinstate the general principles of steroid therapy as the opening paragraph of the DOSAGE AND ADMINISTRATION section, even though we note that the latest editions of competitive oral steroids package inserts bear only the briefer statement which we submitted in our September 14, 1972 submission.

d) The typographical error you discovered in the ACTIONS section will be corrected (mispelling of the word "immune").

NOTE: Four paste-up copies of the package insert showing how we intend to revise it, are included with this submission.

RECEIVED
NOV 24 1972
BUREAU OF DRUGS

Regarding other information required:

1. Please refer to our letter of September 14, 1972, page 2, item (3), where we describe[illegible]

[illegible]

We only recently undertook the project of assigning expiration dates to all of our products. Prior to that time, we assigned expiration dates only to products with expected shelf lives of less than three years. In all of our testing, few drugs have shown greater stability than ORASONE Tablets. Somewhere in this area one has to allow for judgment - especially in view of our lack of control over storage conditions in the pharmacies. We believe we are fully qualified to make judgments based on our experience with our own formulations, and we are convinced that an expiration dating period of three years for ORASONE Tablets is a valid one.

We trust that this submission, along with Mr. Pendergast's letter regarding the 10 mg. and 20 mg. potencies, fulfills the requirements for approval of NDA 83-009.

Yours truly,

ROWELL LABORATORIES, INC.

Ben E. Greenwell

Ben E. Greenwell, Ph.D.
Vice President, Scientific
and Regulatory Affairs

BEG:dat

NDA 83-009

AF 20-333

FEB 15 1973

Rowell Laboratories, Inc.
Attention: Dr. Ben E. Greenwell
Baudette, Minnesota 56623

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orasone (prednisone) Tablet, 1 mg. and 5 mg.

We acknowledge receipt of your communication dated November 21, 1972, amending the application, and a communication dated November 20, 1972, submitted on your behalf by McMurray and Pendergast of Washington, D.C.

Reference is also made to our letter of November 8, 1972.

We have completed the review of this abbreviated new drug application as amended, and have the following comments regarding the proposed labeling:

1. Container labels: Submit revised copies (for the 1 and 5 mg. potencies) in accord with our previous comments regarding the specific dosage statement.

2. Package insert: Submit a revised package insert with references to 10 and 20 mg. tablets deleted - as per our comments of November 8, 1972.

Regarding stability, it is requested that you submit appropriate data (as per our comments of November 8, 1972), if you elect to include the proposed expiration dated on the revised container labels (as above).

Please let us have your response promptly.

cc: MINN-DO
Dup

Sincerely yours,

/S/ 2/14/73

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

1/4/73

2/5/73

Original

ORIG NEW CORRES

McMURRAY AND PENDERGAST

1019 19TH STREET, N. W.

WASHINGTON, D. C. 20036

(202) 833-2550

RAYMOND D. McMURRAY
WILLIAM R. PENDERGAST
DAVID J. KERA

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NEW YORK BAR

CHARLES W. WHITMORE
VIRGINIA BAR
OF COUNSEL

March 15, 1973

Marvin Seife, M.D.
Director
Division of Actions Implementation
DESI Project Office
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: NDA 83-009
ORASONE

Dear Doctor Seife:

This is in reply to your letter of February 15, 1973, to Rowell Laboratories, Inc. regarding the above new drug application. As your files reflect we are counsel to Rowell Laboratories, Inc. with respect to this NDA.

Your letter of February 15 is wholly inadequate as a response to our letter of November 20, 1972, and Rowell Laboratories' letter of November 21, 1972. In our November 20 letter we point out legal and factual reasons why 10-20 mg. dosages of prednisolone are properly covered by DESI announcement 7750. We discuss in detail our position on the impact of the "related" drug regulation to such DESI announcements, as well as our position that a 10-20 mg. dosage is encompassed within the 60 mg. daily dosage permitted by DESI 7750. Your letter of February 15 makes absolutely no reply to these arguments and simply reiterates the earlier conclusion that the 10 and 20 mg. dosages must be deleted. As I am sure you can appreciate, it is rather difficult for us to determine what future course of action to take, if any, since we are not informed as to the factual or legal basis for your conclusion. We would be happy to meet with your representatives at the earliest possible moment to discuss this matter.

When such a meeting is held we believe it would also be pertinent to note that DESI announcement 7750 specifically covers a 16 mg. dosage for Medrol (Upjohn NDA 11-353), Methylprednisolone tablets, which are identical, in potency, to 20 mg. Prednisone tablets. The FDA dosage and administration guidelines, a copy of which is attached, specifically recognize the equivalency of 16 mg. Methyl-prednisolone to 20 mg. Prednisone. Furthermore, DESI 7750 provides for identical labeling for all oral Glucocorticoid drugs, and, thus, Orasone 20 mg., being equal in potency to an NDA drug which is specified in DESI 7750, is "related" to that drug and therefore subject to an abbreviated NDA.

The impact of the related drug regulation on DESI announcements is a matter of major importance, not just for Rowell Laboratories, Inc., but for the whole drug industry, and we believe that each instance where it is to be applied requires the most careful evaluation. To that end, we should like to meet and discuss this with you at your earliest convenience so that a scientifically fair, and legally proper, decision can be made.

If you will have someone call this office we shall make ourselves available for such a meeting.

Very truly yours,

William R. Pendergast

Enclosure
WRP/bmd

NDA 83-009
AF 20-333

NOV 8 1972

Rowell Laboratories, Inc.
Attention: Dr. Ben E. Greenwell
Baudette, Minnesota 56623

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orasone (prednisone) Tablets, 1 mg. and 5 mg.

We acknowledge receipt of your communication dated September 14, 1972, amending the application.

Reference is also made to our letter of July 18, 1972.

We have completed the review of this abbreviated new drug application as amended, and have the following comments regarding the proposed labeling:

1. Container labels: Withdraw the labels for the 10 and 20 mg. tablets, as per our letter of July 18, 1972.

2. Package insert:
   a) Delete the references to 10 ang 20 mg. tablets (as above).
   b) Revise the insert so that the PRECAUTIONS section precedes the section on ADVERSE REACTIONS.
   c) Reinstate the general principles of steroid therapy, as per the enclosed Federal Register announcement of October 21, 1970.
   d) Correct the misspelling of the word "immune" in the ACTIONS section (2nd. paragraph, 2nd. line).

Other information required by section 130.4(f) of the regulations:

1. Include procedures that are adequate to assure the identity, strength, quality and purity of

2. Regarding stability, we have reservations as to the adequacy of the stability data submitted. If you elect to include an expiration date on the labeling, data for the formulation marketed (as per the revised manufacturing procedure) should be submitted as part of this abbreviated new drug application.

Please let us have your response promptly.

Sincerely yours,

11/8/72

Marvin Kaiffe, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

Enclosure
F.R. announcement

cc:
MTNN-DO

ISI

mmj 11-7-72
per 11/8/72

NDA 83-009
80-299
AF 20-333

JUL 18 1972

Rowell Laboratories, Inc.
Attention: Dr. Ben E. Greenwell
Baudette, Minnesota 56623

Gentlemen:

Reference is made to your abbreviated new drug application dated April 14, 1972, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orasone (prednisone) Tablets, 1 mg., 5 mg., 10 mg., and 20 mg.

We have completed the review of this abbreviated new drug application and have the following comments regarding the proposed labeling:

1. Container labels: Delete the specific dosage information and substitute, "Usual Dosage: See Package Insert."

2. Package insert:

   a) In the INDICATIONS section, revise the typography of subsection #2, as per the Federal Register announcement of October 16, 1971.

   b) Revise the DOSAGE and ADMINISTRATION section (that part following the first six paragraphs) to conform to labeling guidelines.

   Materials pertaining to these revisions are enclosed for your convenience.

It is also noted that your application provides for 10 and 20 mg. potencies. Since the Federal Register announcement of October 21, 1970, does not provide for these potencies, such a formulation is not acceptable for an abbreviated new drug application and a full new drug application would be required.

Other information required by section 130.4(f) of the regulations:

1. A statement as to 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.

2. Clarify the analytical procedures used to assure that the components and the final dosage form will comply with the specifications and tests described in U.S.P. XVIII, since it is noted that:

   a) You reference a "foreign steroids" test for prednisone; but this procedure is not part of compendial specifications.

   b) Neither the (1) identification (2) related foreign steroids nor (3) assay procedures for the finished dosage form are in accord with those described in the compendium.

3. Clarify the discrepancy between the per tablet weight listed on your formula sheets and that listed in your "Master Formula-Quality Control Department" sheet.

4. It is noted that although you make reference to a three year expiration date for these preparations, your application omits a full description of, and the data derived from, studies of the stability of the drug.

It is also noted that an earlier communication pertaining to your Prednisone preparation has been given the reference number 80-299. That number is being replaced by the reference # 83-009.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 7/18/72

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

cc:
MIN-DO
Dup

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7/72

NDA 83-009

AF 20-333

MAY 30 1973

Rowell Laboratories, Inc.
Attention: Dr. Ben E. Greenwell
Baudette, Minnesota 56623

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orasone (prednisone) Tablets, 1 mg. and 5 mg.

We acknowledge receipt of a communication dated March 15, 1973, submitted on your behalf by McMurray and Pendergast of Washington, D.C.

This communication re-requested guidance regarding the suitability of filing abbreviated new drug applications for 10 and 20 mg. potencies of prednisone.

In accord with our previous comments, the following is noted:

> Since (1) provision has not been made for the 10 and 20 mg. potencies to be filed as abbreviated new drug applications in any FEDERAL REGISTER announcement and (2) these potencies are not in accord with the potencies of the applicable reference drugs, the application as submitted with regard to these potencies is not acceptable.

If you elect to file for these potencies, a full new drug application——including applicable efficacy and safety data (as per the comments in the FEDERAL REGISTER announcement of October 31, 1972)——should be appropriately submitted.

That part of the material submitted for these potencies will not be reviewed. However, it will be retained in our files.

cc:
MINN-DO

Sincerely yours,

/S/ 5/21/73 Marvin Seife 5/29/73

Marvin Seife, M.D.
Director
Division of Actions Implementation
Drug Efficacy Study Implementation
Project Office
Bureau of Drugs

NDA 83-009
AF 20-333

Rowell Laboratories, Inc.
Attention: Dr. Ben E. Greenwell
Baudette, MN 56623

NOV 14 1973

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orasone (prednisone) Tablets, 1, 5, 10 and 20 mg.

We have re-reviewed the material submitted. However, before we are able to reach a final conclusion, the following additional information is necessary:

1. Regarding labeling:

   a) Revised container labels in accord with our previous comments regarding the specific dosage statement.

   b) Printed inserts in accord with the drafts submitted in your communication of November 21, 1972.

2. Regarding stability, we suggest that you submit a signed statement that you will check the stability of production batches of the preparation, submit results as they become available, and promptly withdraw from the market any lots that may become subpotent.

Please let us have your response promptly.

Sincerely yours,

Marvin Seife 11/13/73

Marvin Seife, M.D.
Director
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs

cc:
MINN-DO

11/13/73
12-73 T. Barany 11-13-73

R/w/P 0216

RESUBMISSION
NDA ORIG AMENDMENT

FPL

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ROWELL LABORATORIES, INC.

BAUDETTE, MINNESOTA 56623 218/634-1866

BEN E. GREENWELL, Ph. D.
VICE PRESIDENT, RESEARCH

September 14, 1972

Marvin Seife, M.D., Director
Division of Actions Implementation
DESI Project Office
Food and Drug Administration
Rockville, Maryland 20852

Ref: NDA 83-009; Your letter of July 18, 1972.

Dear Doctor Seife:

In reply to your letter of July 18, 1972, which listed a number of deficiencies in our Abbreviated NDA (83-009) for ORASONE Prednisone tablets, I shall discuss all of the points below, in the order in which they appeared in your letter.

Regarding proposed labeling:

(1) We shall revise our container labels, as you suggested, by replacing the specific dosage statement with the statement: "Usual Dosage: See Package Insert." This will be done at the next printing, and when completed, we shall submit 12 copies for your files.

(2) Our package insert has been revised in a way that I think will satisfy your requirements. Actually, this was done prior to our submission of the application dated April 14, 1972, but I was not apprised of the changes. Twelve copies of the printed insert that we currently are using are attached. These now comply with all of the FEDERAL REGISTER announcements as we interpret them.

Provision for 10-mg. and 20-mg. potencies:

Reviewing DESI 7750, Part B, we find that there is no limitation as to tablet strength. The official "Dosage and Administration" guidelines, enclosed with your letter of July 18, 1972, recommend [illegible] mg. of prednisone as an initial daily dose. Ten- and 20-mg. potencies are perfectly in order for dosages of this magnitude. We fail to understand how the Administration can justify the position that DESI 7750 precludes acceptance of 10-mg. and 20-mg. tablets via the abbreviated NDA procedure.

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SEP 18 1972
BUREAU OF DRUGS

Furthermore, such an interpretation goes against FDA's proposed regulation 130.40 (b), (Federal Register, Feb. 10, 1972), which states its intention to apply DESI announcements to related drugs including "other brands, potencies, dosage forms, salts and esters" of the drug covered by the DESI announcement (underline supplied). ORASONE 10-mg. and 20-mg. tablets

clearly are related drugs that fit the situation covered by the proposed regulation. For these reasons, we do not intend to withdraw ORASONE 10-mg. and 20-mg. tablets from this submission.

Other information required (p. 2 of July 18, 1972 letter):

(1) Please amend NDA 83-009 to specify that ORASONE Tablets are limited in their labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer them.

(2) We have changed our tests and specifications for Prednisone Powder and for ORASONE Tablets to comply with the USP XVIII monographs, with the following exceptions: (a) We conduct the Related Foreign Steroids test on Prednisone Powder and not on ORASONE Tablets. Thus, we assure that the raw material is free of excess foreign steroids, which obviates the need to test the finished tablets. (b) We do not conduct the test for Selenium in Prednisone Powder. (c) We have an internal specification for Disintegration Time of ORASONE Tablets, not called for in the official compendium.

(3) The discrepancy in tablet weights listed on our Master Formula sheets versus those on our Product Specification Sheets is explained by the fact that a minor formula change (to correct a capping problem) was instituted after I had collected the Master Formula sheets for the submission. Enclosed are replacements for pages 1, 5a, 5c, 5e, and 5g of our original submission, which provide the correct list of components and the current Master Formula sheets. You will note that (, p. 143) and (XVIII, p. 515) have been added to the formulations. Please add these two ingredients to the list of official ingredients in paragraph 2, page 3 of our original submission. The tablet weights given in our Product Specifications sheets (pages 3a, 3c, 3e, and 3g) are correct as given in the original submission.

(4) Regarding our 3-year expiration date:

We marketed Prednisone Tablets in 1958, using a procedure of of a prednisone- e blend with followed by blending with rior to compression. As you will note, our current formulations for ORASONE Tablets are very similar to the original formulations, the only changes being that we have added to the prednisone blend; to the solution for in place of ; and two of the formulations.

Thus, it is our opinion that stability data from aged production batches of the old formulations provide useful information relative to our current formulations. Also, prednisone is known to be highly stable in such neutral, dry dosage forms.

Our expiration date of 3 years is based on data that show that 3-yr. old production batches of 1-mg. and 5-mg. Prednisone Tablets of our manufacture (formula given before) have maintained disintegration times, dissolution rates, and potencies well within USP limits. See Attachments No. 1 and No. 2 stapled to this letter.

Additionally, we have four lots of the current formulations on stability test both at R.T. and at 45°C. Interim assays obtained by the USP XVIII method are given below:

Lot No.	Initial Assay	Assay after 8 mos. R.T.	Assay after 8 mos. 45°C
58535	102.4%	97.5%	97.1%
58487	97.4%	101.8%	98.6%
58500	100.3%	96.7%	101.6%
58499	100.5%	101.5%	110.0%

As expected, these tablets display excellent stability of the active ingredient. Our study will be continued indefinitely, and we fully expect at some future date to find justification to extend the expiration date beyond 3 years.

We trust that this fulfills the requirements for approval of NDA 83-009.

Yours truly,

ROWELL LABORATORIES, INC.

Ben E. Greenwell

Ben E. Greenwell, Ph.D.
Vice President, Scientific
and Regulatory Affairs

BEG:dat

Enclosures