

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
40287

CORRESPONDENCE

Halsey Drug Company, Inc.
Attention: George F. J. Scholes
1827 Pacific Street
Brooklyn, New York 11232

DEC 22 1997



Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated November 24, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Prednisolone Syrup USP, 15 mg/5 mL.

Reference is also made to the telephone conversation dated December 12, 1997 and your correspondence dated December 15, 1997.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(2) for the following reasons:

The concentration of the inactive ingredient, Flavor Cherry WL-1093 in your proposed drug product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in an oral drug product. Therefore, the proposed drug product cannot be accepted for filing as an ANDA. Please provide examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration range or provide information demonstrating that this inactive ingredient in this concentration does not affect the safety of the proposed drug product.

Please revise the qualitative and quantitative composition statement to reflect the concentration of the ingredients per five milliliters. Also, please revise the comparative composition statement to reflect the correct concentration of Propylene Glycol and Benzoic Acid per five milliliters and Flavor Cherry WL-1093 per ANDA batch.

In addition, please provide the address of the active drug substance manufacturer as well as the addresses of all inactive ingredient manufacturers.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Gregory S. Davis
Project Manager
(301) 827-5862

Sincerely yours, /

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc ANDA 40-287
DUP/Jacket
Division File
HFD-92
Field Copy
HFD-600/Reading File
HFD-610/JPhillips
HFD-615/MBennett

... /
ANDAs Refuse to File!

ANDA 40-287

Halsey Drug Company, Inc.
Attention: George F. J. Scholes
1827 Pacific Street
Brooklyn, New York 11232

APR 20 1998

|||||

Dear Sir:

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

Reference is made to our "Refuse to File" letter dated December 22, 1997 and your amendment dated March 20, 1998.

Reference is also made to the telephone conversations dated December 12, 1997, December 16, 1997 and April 10, 1998 and your correspondence dated December 15, 1997, December 17, 1997, December 30, 1997, April 9, 1998 and April 13, 1998.

NAME OF DRUG: Prednisolone Syrup USP, 15 mg/mL

DATE OF APPLICATION: November 24, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 23, 1998

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 ANDA number shown above.

Should you have questions concerning this application, contact:

Jim Wilson
Project Manager
(301) 827-5848

Sincerely yours,



Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-287
cc: DUP/Jacket
Division File
Field Copy
HFD-610/J. Phillips
HFD-92
HFD-615/M. Bennett

ANDA Acknowledgment Letter!

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

FA
TELEPHONE AMENDMENT

Attn: Ms. Bonnie McNeal
Via fax: 301-594-0180

TELEPHONE AMENDMENT

**RE: Prednisolone Syrup USP, 15mg/5ml
ANDA 40-287**

Dear Mr. Sporn:

Our counsel, Jim Rubin, and I have had several conversations with Ms. Bonnie McNeal and Dr. Sayeed of your office concerning the above ANDA. It is our understanding that Dr. Sayeed would like to see antimicrobial effectiveness data at % below the product's minimum specified preservative content of %.

Therefore, we prepared a proportional scaled-down batch of the syrup with the exception of the Benzoic Acid, which was formulated at % of the labeled amount of 5mg/5ml. (The preparation was assayed for Benzoic Acid and yielded % of the labeled claim.)

The % preservative product was tested pursuant to the USP XXIII, Eighth Supplement under <51> ANTIMICROBIAL EFFECTIVENESS TESTING. I am attaching a table which shows the results at the required time intervals. However, in summary, the data clearly demonstrate that Halsey's Prednisolone Syrup meets compendial requirements for antimicrobial effectiveness for Category 1C Products at % of labeled claim preservative. In particular, the USP requires "Not less than log reduction of bacteria from the initial count at 14 days, and no increase from the 14 days count at 28 days." Our % preservative product had a **greater than log reduction from initial count at 14 days and no increase at 28 days.** Regarding Yeast and Molds, the USP requires "No increase from the initial calculated count at 14 and 28 days." Our product showed a **reduction from initial count at 14 and 28 days.**

Based upon the above information, we believe that our ANDA for Prednisolone Syrup is ready for approval. If you or your staff have any questions, please contact Jim Rubin at 201-869-6151 or me at 201-861-7815.

Thank you in advance for your considerations.

Sincerely,

Jeryl D. Rubin

Jeryl D. Rubin
Vice President, Corporate Compliance

Att.

RECEIVED

MAY 13 1999

GENERIC DRUGS

phone: 718.467.7500

1827 Pacific Street, Brooklyn, NY 11233

fax: 718.467.4261

Halsey *The New*
Drug Company, Inc.

March 4, 1999

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/FA

Attention: Mark Anderson, Project Manager

NDA ORIG AMENDMENT

FACSMILE AMENDMENT
(Hard copy w/attachments to follow)

RE: ANDA # 40-287
Prednisolone Syrup, USP (15 mg/5 mL)

Dear Mr. Anderson,

Reference is made to your facsimile letter dated February 16, 1999 concerning our Abbreviated New Drug Application dated September 25, 1998 for Prednisolone Syrup, 15 mg/5 mL. Halsey is hereby responding to the deficiencies in full.

The reviewer's deficiencies are transcribed in bold lettering followed immediately by Halsey's response in normal type and supported by numbered attachments as needed.

Deficiencies:

38. Facsimile deficiencies

- 1. Your release documentation for the final drug product needs to include the specification/limits for degradants/impurities testing. We recommend the inclusion of the same limits proposed in your Stability Protocol.**

Halsey agrees and hereby submits the revised specifications/limits for degradants/impurities testing. We are including the same limits as those proposed in our Stability Protocol, which is already in our application. Please see Attachments I and II.

- 2. Please provide antimicrobial preservatives effectiveness data to demonstrate that the preservative, (i.e. benzoic acid) is effective at % of its labeled concentration in the drug product.**

The antimicrobial effectiveness study was performed according to the procedure as described in USP XXIII, i.e. at 100 % of the labeled concentration of the preservative, Benzoic Acid. The Antimicrobial Preservatives Effectiveness Test at % of the labeled concentration is not part of the release criteria.

phone: 718.467.7500

1827 Pacific Street, Brooklyn, NY 11233

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therefore should not have been included in our submission. We apologize for its inadvertent inclusion, and have revised the protocol. Please see Attachment III.

Included also for your review are the antimicrobial effectiveness results for the 18-month stability sample for the submission batch. Please see Attachment IV.

1. General Comments

- i. **Due to changes in the approved labeling of the reference listed drug (Muro Pharmaceuticals, Inc. approved August 5, 1998; revised May 1998), we ask that you revise your labeling accordingly.**

These changes will be noted in the appropriate side-by-side label and labeling comparisons. Please see attachment V.

- ii. **We note that you have not submitted a properly signed and executed application form with this submission, as required under 21 CFR [314.50 (a)]. We refer you to the regulations for further guidance.**

Halsey believes that it already has submitted a signed and executed application form for this application. Please see attachment VI.

2. Container – 8 ounce (236 mL) and 16 ounce (473 mL) bottles.

Container labels have been changed accordingly. Please see attachment V.

3. Insert

a. Description

We note that you inadvertently included both chemical names in your draft package insert. The second name is preferable as follows:

11 β , 17, 21-Trihydroxypregna-1, 4-diene-3, 20-dione (anhydrous)

These changes will be noted in the appropriate side-by-side label and labeling comparisons. Please see attachment V.

b. Indications and Usage

Respiratory Diseases: Delete the term

...Used concurrently with appropriate chemotherapy.

These changes will be noted in the appropriate side-by-side label and labeling comparisons. Please see attachment V.

c. **Warnings**

- i. **Revise the format to make the fourth paragraph referring to the "Use in Pregnancy" the last paragraph of this section.**

These changes will be noted in the appropriate side-by-side label and labeling comparisons. Please see attachment V.

- ii. **Seventh paragraph, first sentence – revise to read as follows:**

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals.

These changes will be noted in the appropriate side-by-side label and labeling comparisons. Please see attachment V.

- iii. **Delete the eighth paragraph**

These changes will be noted in the appropriate side-by-side label and labeling comparisons. Please see attachment V.

d. **Precautions**

Revise format and make the first paragraph, "Information for Patients:", the last paragraph of this section.

These changes will be noted in the appropriate side-by-side label and labeling comparisons. Please see Attachment V.

Halsey has provided side-by-side label comparison with the corrections listed above and noted in the margin. Halsey has sent these instructions to the printer and the final printed label is submitted. Please see attachment V.

We believe that the information submitted should allow you to complete your review. If further discussion is required, please do not hesitate to call me at (718) 467-7500 ext. 265.

Sincerely,
Halsey Drug Co., Inc.



George Scholes
Vice President, Regulatory Affairs



Halsey Drug Co., Inc.
Prednisolone Syrup
ANDA 40-287

SALES
OFFICE

CORPORATE
OFFICE

1827 Pacific Street
Brooklyn, NY 11233
(800) 252-5230
(718) 467-7500
FAX (718) 467-4261

245 Old Hook Road
Westwood, NJ 07675
(800) 237-9939
(201) 358-6282
FAX (201) 358-1976

September 25, 1998

Mark Anderson, Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/A/C

RE: PREDNISOLONE SYRUP, USP, 15 mg/5 mL
ANDA 40-287

Dear Mr. Anderson:

Reference is made to our Abbreviated New Drug Application for Prednisolone Syrup, USP 15 mg/5 mL and your Major Amendment fax/letter dated August 6, 1998. Halsey is hereby responding to the deficiencies in full.

The reviewer's deficiencies are transcribed in bold lettering followed immediately by Halsey's response in normal type and supported by numbered attachments as needed. We are responding to 8 chemistry, manufacturing and control deficiencies and acknowledge our analytical methodology is not identical to the US Pharmacopeial methods. Our revised draft labeling is contained in Exhibit C.

We feel confident that the information submitted will allow you to complete your review. If further discussion is required, please do not hesitate contacting me or Ms. Ann Young at 718-467-7500.

Very truly yours,

George F. J. Scholes
Vice President - Regulatory Affairs

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A. Deficiencies:

- 1. There are too many errors in the formula extensions (g/Kg designations and wrong calculations for Propylene Glycol and Benzoic Acid for the Liter batch) shown on pages 95/96/111/536B/536C of your application and in Exhibits 3 and 4 of your March 20, 1998 correspondence to the Agency. Please review and correct these Tables and re-submit them.**

RESPONSE:

We apologize for the apparent errors. R & D is now following strict convention to provide weights and measures in the same units and to be aware of significant figures and scale/balance/measure sensitivities. The VP of Quality Control is now directly and solely responsible for checking these calculations. Again, personnel changes in Regulatory Affairs may have allowed these corrections to go undone. In Exhibit 1, please find corrected pages: 95, 96, 111, 536B and 536C from the original submission and Exhibits 2 and 4 from the March 29 correspondence.

The values for propylene glycol and benzoic acid were not calculated incorrectly, but were entered in the tables incorrectly. See Exhibit A1.

A.2. You have shown a % overage in the label amount of Prednisolone, USP in your drug product manufacture documents. An overage of % Prednisolone is not recommended. Please reformulate your components and composition section to 100 % of the labeled amount of Prednisolone and submit the appropriate documentation.

RESPONSE:

The original R & D group had determined that in the initial pilot batch there had been some Prednisolone loss due to transfer from dissolution in alcohol to blending in the mixing container. This overage was not intended to contend with a stability problem, but was included to assure 100 % label claim in the initial testing of the finished product solution. Subsequent R & D batch procedures were able to eliminate the transfer problem, but we failed to annul the overage. Halsey provides the new formulation page with the Prednisolone formulated to 100 % of the label claim. See Exhibit A2.

- A3. The information which you have supplied regarding resin is incomplete. In order to use this material, you should supply information regarding its suitability in containers which contains foods/drugs. This information can be supplied directly as an amendment to this application or by reference to Drug Master File.**

Response:

We herewith enclose copy of letter to the Food and Drug Administration wherein authorization to reference their DMF Pages 18-30 and Appendices 8-20 is provided on behalf of Halsey Drug Company Inc. See exhibit A3.

- A4. Your in-process protocol on page 348 of your application indicates samples are taken from the top/bottom of the bulk tank and only a single set of data are shown. Are the data an average of several values or are the samples mixed before testing? Please provide test data from each sample.**

Response:

The In-Process Control Protocol form for validation purposes was inadvertently utilized.

The data submitted are single values of the sample taken at the start up of the test batch. Since a test batch was liters it takes less than a day to process. Therefore, the only sample taken was at the beginning and end of the packaging process. The data presented was from the start up sample only.

- A7. Your Microbiology Protocol for Performing Anti-microbial Preservatives as shown on pages 552-555 to use Benzoic Acid as a preservative is incomplete. Please submit these data. You will also need to include Benzoic Acid content as part of your drug product release testing and Stability Protocol.**

Response:

We herewith enclose our revised Microbiology Protocol for "Performing Anti-Microbial Preservatives effectiveness". Please note the revision:

IV Procedure

The inoculated containers which were kept at 20°C to 25°C, as per the procedure shall be examined at 0, 7, 14, 21 and 28 days.

NOTE: The inclusion of time 0 to this procedure.

Also attached is our Certificate of Analysis for Anti Microbial Preservatives Effectiveness Test. See Exhibit A7.

- A8. Please establish a test/specification for individual and total degradants in your Stability Protocol. These requirements should be established based on data from your exhibit batch.**

Response:

We herewith enclose our revised Stability Protocol for this product. Please note testing for degradants has been included, please refer to:

IV Procedure

D. Type of Testing and Specification

6. Degradants	Individual:	Not more than	%
	Total:	Not more than	%

See Exhibit A8.

- A9. Please submit any room temperature stability test data which you may have available for the exhibit lot, Lot #7G07E.**

Response:

We herewith enclose room temperature stability data for 3, 6, 9 and 12 months for our package sizes of 8oz and 16oz. See Exhibit A9.

- B. Halsey's analytical methodology is not identical to the U Pharmacopeial method for the final drug product. Halsey understands that the USP methods are the regulatory methods and will prevail in the event of any dispute. See Exhibit B.

**APPEARS THIS WAY
ON ORIGINAL**

CORPORATE
OFFICE

1827 Pacific Street
Brooklyn, NY 11233
(800) 252-5230
(718) 467-7500
FAX (718) 467-4261

245 Old Hook Road
Westwood, NJ 07675
(800) 237-9939
(201) 358-6282
FAX (201) 358-1976

November 24, 1997

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

**ORIGINAL ABBREVIATED NEW DRUG APPLICATION
PREDNISOLONE SYRUP, 15 mg per 5 mL**

Dear Mr. Sporn:

Pursuant to Section 505j of the Food, Drug and Cosmetic Act and in compliance with 21 CFR 314.94, Halsey Drug Company, Inc. herewith submits an Abbreviated New Drug Application (ANDA) for:

Prednisolone Syrup, 15 mg per 5 mL

In support of this Application, the information outlined below is provided:

- Table of Contents and Checklist for Completeness and Acceptability
- Application Form FDA 356h
- Basis for Submission
- Appropriate Patent and Exclusivity Certification and Commitments
- Comparison between the proposed drug:
Prednisolone Syrup, 15 mg per 5 mL
And the reference listed drug:
*Prelone® Syrup (Prednisolone Syrup, 15 mg per 5 mL)
manufactured by Muro Pharmaceuticals.*
- Draft labels/labeling and a side-by-side comparison of the proposed draft with the approved reference listed drug label and labeling.
- Bioequivalency is self evident and is demonstrated by data in the application based on the information that the drug product is:
* A solution or oral syrup dosage form, containing the same concentration of active ingredient, in the same dosage form.

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and contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application that may significantly affect absorption of the active drug ingredient or active moiety.

- Chemistry, manufacturing and controls information
- Methods Validation package (one copy in the archival [blue] binder, one copy in the review [red] binder.
- Debarment Certification

This ANDA consists of one volume. Halsey Drug Company, Inc. is filing an archival copy [blue], technical review copy [red] and a separate copy of the bioequivalence section. Two additional, separately-bound copies of the methods validation section are provided.

Several summary tables are included in the executive summary immediately following this letter.

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of this filed with the Office of Generic Drugs) was sent to our local district office. This "field copy" is bound in a burgundy folder.

Halsey Drug Company, Inc. requests that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

I am confident that the information provided is complete and approvable, if any question does arise, please do not hesitate to call me at (718) 467-7500 or fax (718) 493-1575

Signed on behalf of Halsey Drug Company, Inc.

Sincerely,

 **GENERIC DRUGS**

George F.J. Scholes
Vice President, Regulatory Affairs

Enclosures

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DEC 02 1997

Executive Summary

This application is submitted and owned by Halsey Drug Company, Incorporated of 1827 Pacific Street, Brooklyn, New York 11233. The regulatory division of Halsey Drug Company is located at the same address, all inquires, and correspondence may be directed to this address.

This Abbreviated New Drug Application has been prepared to comply with the suggested format of the recent Guidance dated April 1997, which replaces the Office of Generic Drugs (OGD) Policy and Procedure Guide (PPG) 30-91, with a few minor modifications. This application also complies with PP&G 22-90, the Inactive Ingredients list, and OGD Letter to Industry of August 4, 1993 for batch size.

The modifications or significantly unique aspects of this application are briefly discussed below. A set of concise tables accompanies this summary and will be repeated at the beginning of each volume of this submission for ease of reference.

Section I includes a complete signed copy of Form FDA 356h with a list of all referenced applications and master files. The form also indicates the correct name of the applicant and the correct address for all correspondence as discussed above. This section also includes the appropriate certification for the submission of Field Copy as required under 21 CFR 314.94 (d)(5).

A *No Relevant Patent Certification* {21CFR314.94(a)(12)(ii)} stating that no relevant patent claims the listed drug product or claims the use of the listed product and a certification of no known exclusivity are presented in Section III based on the listed information in most current supplement of Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). Halsey notes that Muro Pharmaceuticals Prelone® Syrup (Prednisolone Syrup, USP 15 mg/5ml) is the product used as the basis for this application. There are no patents or rights to marketing exclusivity listed for this application.

There are no in-vivo or in-vitro studies enclosed with this application. A bioequivalence waiver request as permitted under 21 CFR 320.22(b)(3) is found in Section VI. Additional information in Section VI includes the formulation comparison for reference listed drug and the proposed product subject of this application. Information on the inactive ingredient {21 CFR 314.94(a)(9)(ii)} to demonstrate that there are no safety issues due to the use of the proposed inactive ingredients are presented in this section and Section VII.

Section XI describes the manufacturing process

Section XII contains the information on the executed batch, Lot 7G07E. The initial blend size was liters. The production batch does not exceed the allowed amount of 5 X's the test batch. In section XIII, Container Closure Systems, there are four packaging configurations on stability. Section XIV and XV contain in-house identification testing of the finished product.

**APPEARS THIS WAY
ON ORIGINAL**

ANDA 40-287
Prednisolone Syrup USP, 15mg/mL



CORPORATE
OFFICE

SALES
OFFICE

327 Pacific Street
Brooklyn, NY 11233
(800) 252-5230
(718) 467-7500
FAX (718) 467-4261

245 Old Hook Road
Westwood, NJ 07675
(800) 237-9939
(201) 358-6282
FAX (201) 358-1976

March 20, 1998

Mr. Peter Rickman, Branch Chief
Regulatory Support Staff
OGD (HFD - 600)
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

NDA ORIG AMENDMENT
N/AC

Prednisolone Syrup USP, 15 mg/5 mL
Request to File based on additional information

In reference to our Abbreviated New Drug Application for Prednisolone Syrup USP, 15 mg / 5 mL dated November 24, 1997, the FDA Refuse to File (RTF) letter of December 22, 1997 and our RTF Correspondences of December 15, 17, and 30, 1997; Halsey wishes to amend the application based on the information that the Agency has suspended the Inactive Ingredient regulation while considering changes to the rule.

Halsey would like to thank you for this opportunity to provide additional safety information for the Cherry Flavor to aid the determination of the acceptability of our filing for Prednisolone Syrup. The information includes some of the information submitted in previous correspondence on this subject, but in addition, we have asked the manufacturer of the cherry flavor to list the components and LD50 data if available. An example follows:

Examples of table of components to be provided by _____ under separate cover.

Component	%W/V	LD50/MED	
		mg/kg	(mg/kg) LD50
	%		(mg/kg) LD50
	%		(mg/kg) LD50

Halsey has provide the Office of Generic Drugs (OGD) information about other products that contain _____ cherry flavor. Halsey suspects that most of the components of cherry flavor _____ are listed in the _____ or are components of currently listed cherry flavors. According to the _____ there are two "NDAs," which list Cherry Flavor in addition to Halsey's Promethazine (ANDA _____). Also the _____ does not list _____ for this flavor, but does list a range for Cherry Flavor in general. Halsey also feels that the CODE based on Hatch-Waxman Act Section 505(j)(3)(H) requires the inactives be safe and _____ is prescribed, recommended, or suggested in the labeling.

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Halsey does know that the FDA approved Halsey's products with a composition of _____ % w/v of cherry flavor WL-1093 (the proposed product lists _____ % w/v). The maximum daily dose of this ingredient would be nearly the same for the proposed product as was the dose in the previously approved products. The IIG does not list these products under the WL-1093 limits, but Halsey assumed that the Cherry flavor limits of _____ % w/v included Halsey's previously approved formulations.

Halsey has requested that _____ the manufacturer of the inactive ingredient to provide any safety information on the composition of this flavor formulation available. _____ has described the product as composed of GRAS components with a general recommended effective level of _____ % in confectioneries and similar products. A letter of Certification allowing _____ to submit information to the application is included in this response.

In response to the FDA letter of December 22, 1997, in which, the FDA states that, "the inactive ingredient, Cherry Flavor WL-1093, in your proposed drug product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in an oral drug product." Halsey has no way of knowing the maximum concentration approved in the NDAs listed for this product, but we can assume that the concentration was equal to or greater than our product's concentration of _____ % w/v. This represents a very slight change of _____ % w/v of the total dose. A representative from the Agency stated that it is a _____ % change in concentration. In fact it is a _____ % greater than the existing Halsey approved concentration, but only a _____ % change in concentration. Using other FDA guides as an example of acceptable changes, the component changes allowed under SUPAC are expressed in % of total formulation. The Inactive Ingredient Guide states, "Potency Range - Specifies the minimum and maximum amounts of inactive ingredients for each route/dosage form." Again, this seems to imply total per dose. The OTC guide for sodium is based on total exposure per day. We realize that this is not a direct correlation, but the amount of change in the context of the whole formulation is actually quite small. We have also provide information that demonstrates the labeling for this product provides a lower daily exposure to this component than our previously approved product. Exhibit 1 & 2

Exhibit 3 & 4, Demonstrates the qualitative and quantitative composition. This is done to reflect the concentration of the ingredients per five milliliters. The comparative composition between test batch and production batch has been revised to reflect the correct concentration of Propylene Glycol and Benzoic Acid per five milliliters and Flavor Cherry WL-1093 per ANDA batch. Addresses of active and inactive drug substance manufacturers are provided in Exhibit 5.

ANDA 40-287
Prednisolone Syrup USP, 15mg/mL

Halsey appreciates your time and consideration in deliberating on this subject. We feel confident that the information submitted will allow a filing of our application. If there is, need for further discussion, please do not hesitate calling me at (718) 467-7500.

Sincerely,

A handwritten signature in black ink, appearing to read "George Scholes". The signature is written in a cursive style with a large initial "G".

George Scholes
Vice President of Regulatory Affairs

ANDA 40-287
Prednisolone Syrup USP, 15mg/mL



SALES
OFFICE

CORPORATE
OFFICE

827 Pacific Street
Brooklyn, NY 11233
(800) 252-5230
(718) 467-7500
FAX (718) 467-4261

245 Old Hook Road
Westwood, NJ 07675
(800) 237-9939
(201) 358-6282
FAX (201) 358-1976

March 20, 1998

Mr. Peter Rickman, Branch Chief
Regulatory Support Staff
OGD (HFD - 600)
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Letter of Certification

This is a letter of certification asking FDA to allowing _____ to submit any pertinent information to ANDA 40-287 (Prednisolone Syrup USP, 15 mg / 5 mL) This information will remain proprietary to _____ and will only be used to assist Halsey in submitting our application.

Sincerely,

George Scholes
Vice President of Regulatory Affairs

cc: R & H Florasynth

BLUE CROSS * CENCI * HOUBA * RACHELLE LABS
HALSEY
DRUG CO., INC.

SALES
OFFICE

245 Old Hook Road
Westwood, NJ 07675
(800) 237-9939
(201) 358-6282
FAX (201) 358-1976

December 30, 1997

Jerry Phillips, Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
Rockville MD 20857

NEW CORRESP

RE: ANDA 40-287
Prednisolone Syrup USP, 15mg/5mL

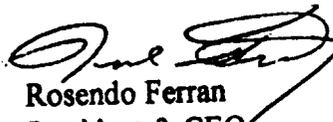
Dear Mr. Phillips:

We acknowledge receipt of the refuse to file letter dated December 22, 1997 for the above referenced ANDA.

We wish to avail ourselves of the opportunity for an informal conference to discuss information that was provided on December 15 and 17, 1997. We are prepared to meet in Rockville anytime convenient to you during the first or second week of January 1998.

Very truly yours,

HALSEY DRUG CO., INC.


Rosendo Ferran
President & CEO

CC: Gregory S. Davis
Project Manager
Office of Generic Drugs

file:ay/c/file/FDA97

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ANDA 40-287
Prednisolone Syrup USP, 15mg/mL



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OFFICE

SALES
OFFICE

1827 Pacific Street
Brooklyn, NY 11233
(800) 252-5230
(718) 467-7500
FAX (718) 467-4261

245 Old Hook Road
Westwood, NJ 07675
(800) 237-9939
(201) 358-6282
FAX (201) 358-1976

April 13, 1998

Mr. Greg Davis
Regulatory Support Staff
OGD (HFD - 600)
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

**Prednisolone Syrup USP, 15 mg/5 mL
Request to File based on additional information**

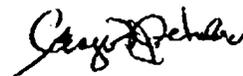
In reference to our Abbreviated New Drug Application for Prednisolone Syrup USP, 15 mg / 5 mL, dated November 24, 1997, the FDA Refuse to File (RTF) letter of December 22, 1997 and our RTF Correspondences of December 15, 17, and 30, 1997; Halsey wishes to amend the application based on the information that the Agency has suspended the Inactive Ingredient regulation while considering changes to the rule.

Halsey would like to thank you for this opportunity to provide additional safety proprietor information supplied to you by _____ on Thursday April 9th for the Cherry Flavor WI.-1093 to aid the determination of the acceptability of our filing for Prednisolone Syrup

As well, we submit exhibit 3 & 4 revised as per your comments. This demonstrates the qualitative and quantitative composition. This is done to reflect the concentration of the ingredients per five milliliters. The comparative composition between test batch and production batch has been revised to reflect the correct concentration of Propylene Glycol and Benzoic Acid per five milliliters and Flavor Cherry WI.-1093 per ANDA batch.

Halsey appreciates your time and consideration in deliberating on this subject. We feel confident that the information submitted will allow a filing of our application. If there is, need for further discussion, please do not hesitate calling me at (718) 467-7500.

Sincerely,



George Scholes
Vice President of Regulatory Affairs