CENTER FOR DRUG EVALUATION AND RESEARCH

75-117

APPLICATION NUMBER:

CORRESPONDENCE

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT
ANDA: 75-117 APPLICANT: Ascent Pediatrics, Inc.

DRUG PRODUCT: Prednisolone Sodium Phosphate 20.2 mg/5 mL (equivalent to 15 mg/5 mL prednisolone)

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT
ANDA: 75-117 APPLICANT: Ascent Pediatrics, Inc.

DRUG PRODUCT: Prednisolone Sodium Phosphate 20.2 mg/5 mL (equivalent to 15 mg/5 mL prednisolone)

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M Saul

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Prednisolone Sodium Phosphate Oral Solution 20.2 mg/5 mL (equivalent to 15 mg/5 mL Prednisolone)	Ascent Pediatrics, Inc. Wilmington, MA
ANDA #75-117	Submission Date:
Reviewer: Lin-Whei Chuang	October 23, 2000

V:\FIRMSAM\ASCENT\LTRS&REV\75117AM.000

Review of Flavor Components

Background:

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

10/23/00

ASCENT PEDIATRICS, INC.

187 Ballardvale Street • Suite B125 • Wilmington, MA 01887 • Phone 978-658-2500 • Fax 978-658-3939

October 23, 2000 ORIG AMENDMENT

N/AM

Dr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Telephone Amendment

ANDA 75-117
Prednisolone Sodium Phosphate
Oral Solution 20.2mg/5mL

Orapred

Dear Dr. Buehler:

Reference is made to our application and to a telephone request made on 10/20/00 by the chemistry reviewer.

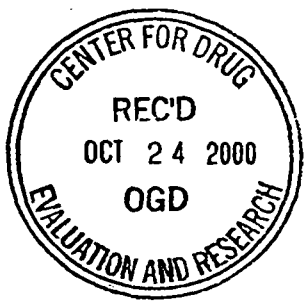
The composition of the flavor (Artificial Flavor) used in our Orapred product was requested. This flavor is provided to . The composition is proprietary and therefore will not provide the composition to us. As is typical in this situation have a Drug Master File with the Agency which provides the composition of the flavor and certification that all components are GRAS food additive ingredients.

Ascent included s letter authorizing reference to D in our initial ANDA submission dated 4/21/97 (page 190A). We have attached a copy of that page for the reviewer's convenience.

We trust that this will adequately address the reviewer's need.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory and Quality Affairs



ASCENT PEDIATRICS, INC.

187 Ballardvale Street • Suite B125 • Wilmington, MA 01887 • Phone 978-658-2500 • Fax 978-658-3939

September 21, 2000

Dr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Telephone Amendment
ANDA 75-117

Prednisolone Sodium Phosphate
Oral Solution 20.2mg/5mL
(equivalent to 15mg/5mL prednisolone)
Orapred

Dear Dr. Buehler: MA ORIG AMENDMENT

Reference is made to our ANDA 75-117, to the Agency's Minor Deficiency letter of 5/1/00, to our Minor Amendment of 7/14/00, and to a telephone discussion with Dr. Takair and Ms. Yu on 9/20/00.

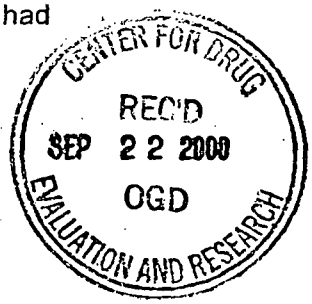
We are hereby amending our application to include a revision to our 7/14/00 response to comment A3 of the Agency's letter of 5/1/00. A revised response to comment A3 is attached.

On 9/20/00, Dr. Takiar requested clarification of our specification limit for related substances for the bulk active prednisolone sodium phosphate (PSP) used in the preparation of our product. The focus of the question was Ascent's response to the Agency's comment A3 of the minor deficiency letter of 5/1/00. It was pointed out that the text of our response indicates that the limit for total related substances is NMT while the attached certificate of analysis (COA) indicates the limit is NMT

We have reviewed our response and have verified that the limit for total related substances is correctly stated as NMT in the COA and that the value in the text of the response is an error.

In further reviewing our response to comment A3, we noted another discrepancy between the text and the COA, specifically the number of identified individual impurities and their individual limits. Here again the COA correctly reflects our intended specification.

Our specification for PSP has been based on the data and information from our supplier, he related substances specification had



originally been set by Ascent using data from elevated temperature storage conditions. Eleven (A through K) identified individual impurities were observed in those studies and individual limits o ere proposed. The first paragraph of the text of our response to comment A3 did not accurately reflect the changes made in the specification. This change was made when tightened its limits for related substances in response to the Agency's request that the specification be based on data for the refrigerated storage conditions that recommends for its material. Based on the data from the reduced storage temperature, seven (A through G) identified individual impurities are observed and the limits for these were individually set. As indicated above, the COA included in our response to comment A3 of the amendment of 7/14/00 correctly reflects our intended specifications and is not changed by this telephone amendment.

We apologize for these errors in our submission and trust that this clarification will resolve the last remaining CMC questions for our application. Please advise by telephone as soon as possible if this is not the case.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory and Quality Affairs

ASCENT PEDIATRICS, INC.

187 Ballardvale Street • Suite B125 • Wilmington, MA 01887 • Phone 978-658-2500 • Fax 978-658-3939

September 29, 2000

ORIG AMENDMENT
N/AM

Dr. Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Telephone Amendment
ANDA 75-117

Prednisolone Sodium Phosphate
Oral Solution 20.2mg/5mL
(equivalent to 15mg/5mL prednisolone)
Orapred

Dear Dr Buehler:

Reference is made to our ANDA and to a telephone discussion with Ms Ruby Yu of the FDA's Office of Generic Drugs on September 29, 2000.

This telephone amendment provides the commitment that Ascent Pediatrics Inc. will cooperate with the Agency to resolve method validation issues that may be revealed by the yet to be completed method validation work conducted by the Agency's laboratory.

Please advise if there is a need for further information.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory and Quality Affairs

ASCENT
PEDIATRICS, INC.

Telephone Amendment
ANDA 75-117

Prednisolone Sodium Phosphate
Oral Solution 20.2mg/5mL
(equivalent to 15mg/5mL prednisolone)
Orapred

Ascent Pediatrics, Inc. commits to cooperate with the Agency to resolve method validation issues that may be revealed to the Office of Generic Drugs when methods validation work is completed.

W.E. Brochu, Ph.D.
Vice President, Regulatory and Quality Affairs

September 29, 2000

ASCENT PEDIATRICS, INC.

187 Ballardvale Street • Suite B125 • Wilmington, MA 01887 • Phone 978-658-2500 • Fax 978-658-3939

July 14, 2000

ORIG AMENDMENT
N/AM.

Gary Buehler
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

MINOR Amendment
Deficiency Response

ANDA 75-117
Prednisolone Sodium Phosphate
Oral Solution 20.2mg/5mL

Orapred

Dear Dr. Buehler:

Reference is made to our ANDA 75-117 and to the Agency's MINOR deficiency letter of 5/1/00.

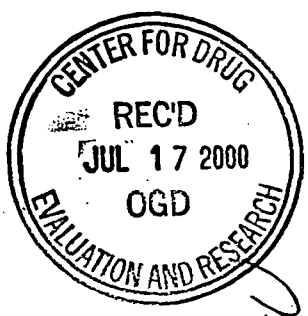
The attached information constitutes a MINOR amendment to our application. This amendment provides complete responses to the deficiencies in our application cited in the Agency's letter. As noted in our response to comment A.1, we have been advised by our supplier for the bulk active ingredient, that they have provided complete responses to the DMF deficiencies cited by the Agency.

Ascent is additionally amending its application to reflect a consolidation of the testing site used by for Orapred finished product and stability evaluation. Ascent has been notified that Oread has closed its Norcross GA facility and transferred all operations to its Lawrence KS facility. Method transfer studies have been conducted for the Orapred analytical procedure. There are no changes being made to the analytical methods. Pertinent information for the Lawrence KS facility location and GMP certification letter is included in this submission.

As always we request the opportunity to discuss and promptly resolve any issues related to the approval of this application that the review team may identify. Please call if I can be of assistance in finally reaching approval for this application.

Sincerely,

W.E. Brochu, Ph.D.
Vice President Regulatory and Quality Affairs



BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT
ANDA: 75-117 APPLICANT: Ascent Pediatrics, Inc.

DRUG PRODUCT: Prednisolone Sodium Phosphate 20.2 mg/5 mL (equivalent to 15 mg/5 mL prednisolone)

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

6.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT
ANDA: 75-117 APPLICANT: Ascent Pediatrics, Inc.

DRUG PRODUCT: Prednisolone Sodium Phosphate 20.2 mg/5 mL (equivalent to 15 mg/5 mL prednisolone)

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT
ANDA: 75-117 APPLICANT: Ascent Pediatrics, Inc.

DRUG PRODUCT: Prednisolone Sodium Phosphate 20.2 mg/5 mL
(equivalent to 15 mg/5 mL prednisolone)

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAY - 1 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-117 APPLICANT: Ascent Pediatrics, Inc.

DRUG PRODUCT: Prednisolone Sodium Phosphate Oral Solution, 20.2 mg/5 mL (equivalent to 15 mg base/5 mL)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File for Prednisolone Sodium Phosphate drug substance has been found deficient. The DMF holder has been informed of the deficiencies. Please do not respond to this MINOR amendment letter until you have been informed by that they have submitted a complete response to the Agency.

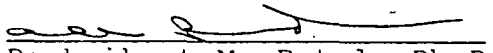
2. Please identify the other residual solvents that make the total limit at no more than 0.5%.

3. Please establish and provide limits for the identified individual unknowns (e.g. A, B, C, D, E, F, G, H, I, J, and K) and explain the difference between "identified individual unknown impurities" and "other unspecified individual unknown impurities". Specification for total impurities is high. Please tighten the limit to be closer to the actual observed value.

4. Drug product release and stability specification for Prednisolone base is high. Please tighten it based on the actual observed values and provide the revised specification for Prednisolone base (mg/5 mL).

5. Please revise your drug product release specifications for deliverable volume to comply with USP 24 <698>.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT
ANDA: 75-117 APPLICANT: Ascent Pediatrics, Inc.

DRUG PRODUCT: Prednisolone Sodium Phosphate 20.2 mg/5 mL (equivalent to 15 mg/5 mL prednisolone)

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-117 APPLICANT: Ascent Pediatrics, Inc.

DRUG PRODUCT: Prednisolone Sodium Phosphate 20.2 mg/5 mL (equivalent to 15 mg/5 mL prednisolone)

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOAVAILABILITY

ORIG AMENDMENT
N/AB

ASCENT PEDIATRICS, INC.

87 Ballardvale Street • Suite B125 • Wilmington, MA 01887 • Phone 978-658-2500 • Fax 978-658-3939

December 14, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

MINOR Bioequivalence Amendment
Prednisolone Sodium Phosphate Oral Solution 20.2mg/5mL
(equivalent to 15mg/5mL prednisolone)
ANDA 75-117
Orapred

Dear Mr. Sporn:

Reference is made to our ANDA #75-117, to our bioequivalence amendment of 9/18/98, and to the Agency's MINOR bioequivalence telephone request made on 12/3/98 to our response on 12/11/98. This amendment provides a correction to the information provided on 12/11/98.

Among the items requested on the Agency's telephone request of 12/3/98 was the analytical potency for the test articles evaluated in the study. We inadvertently provided data for the materials used in Ascent protocol rather than nat was the subject of the current review. The following table provides the analytical potency for the test articles used in Ascent protocol

We apologize for any inconvenience this may have caused.

As requested this information is being sent by fax to the attention of Ms Elaine Hu in the Division of Bioequivalence and is formally being submitted here.

Please advise if there are any additional information needed.

Sincerely,

W.E. Brochu, Ph.D.
Vice President Regulatory & Quality Affairs

RECEIVED
DEC 15 1998
GENERIC DRUGS

ASCENT PEDIATRICS, INC.

187 Ballardvale Street • Suite B125 • Wilmington, MA 01887 • Phone 978-658-2500 • Fax 978-658-3939

December 11, 1998

NDA ORIG AMENDMENT
N/AB

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

MINOR Bioequivalence Amendment
Prednisolone Sodium Phosphate Oral Solution 20.2mg/5mL
(equivalent to 15mg/5mL prednisolone)
ANDA 75-117
Orapred

Dear Mr. Sporn:

Reference is made to our ANDA #75-117, to our bioequivalence amendment of 9/18/98, and to the Agency's MINOR bioequivalence telephone request made on 12/3/98. This amendment provides the requested data and information related to the bioequivalence study report submitted on 9/18/98. The following are provided:
Potency assays for the test and reference products evaluated in the study
Data supporting the stability of prednisolone in plasma after 3 freeze/thaw cycles
Formulations and lot sizes for the test formulations evaluated in the study

As requested this information is being sent by fax to the attention of Ms Elaine Hu in the Division of Bioequivalence and is formally being submitted here.

Please advise if there are any additional information needed.

Sincerely,

W.E. Brochu, Ph.D.
Vice President Regulatory & Quality Affairs

RECEIVED
DEC 14 1998
GENERIC DRUGS

ASCENT PEDIATRICS, INC.

187 Ballardvale Street • Suite B125 • Wilmington, MA 01887 • Phone 978-658-2500 • Fax 978-658-3939

November 19, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville, MD 20855-2773

AMENDMENT
N/AB

RE: ANDA #75-117
Orapred (Prednisolone Sodium Phosphate Oral Solution)
20.2mg/5mL (equivalent to 15 mg/5mL prednisolone)
Bioequivalence Telephone Amendment

Dear Mr. Sporn:

Pursuant to a request made by Ms. Yih Chin Huang on November 18, 1998, please find enclosed a 3.5 inch diskette containing ASCII formatted pharmacokinetic data for the bioequivalence study report submitted on September 18, 1998. The diskette that accompanied the review copy of that submission was apparently lost during shipment. We apologize for any inconvenience this may have caused. For the reviewer's convenience we have also enclosed a printout of the diskette's contents.

Although we are submitting both an archival and review copy of this communication, the above mentioned enclosures accompany only the review copy. Please do not hesitate to contact the undersigned with any questions you may have concerning this communication.

Sincerely,
ASCENT PEDIATRICS, INC.

Mark Murray

Mark Murray
Director, Regulatory Affairs

Enclosure

RECEIVED
NOV 20 1998
GENERIC DRUGS

ASCENT PEDIATRICS, INC.

187 Ballardvale Street • Suite B125 • Wilmington, MA 01887 • Phone 978-658-2500 • Fax 978-658-3939

September 18, 1998

Mr. Douglas Sporn
Director; Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

AMENDMENT
N/AB

Major Amendment - Bioequivalence Study Report
Prednisolone Sodium Phosphate Oral Solution
20.2mg/5mL (equivalent to 15mg/5mL prednisolone)
Orapred
ANDA#75-117

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application and to the Agency's letter of 7/7/98 providing bioequivalency deficiencies.

In response to the Agency's position (point #2 of the Agency's letter of 7/7/98) that the Division is unable to conclude that the inactive ingredient composition of our formulation will not significantly affect the absorption of the active moiety, Ascent is providing the enclosed bioequivalence study report. This report demonstrates the bioequivalence among two different 20.2mg/5mL prednisolone sodium phosphate (PSP) formulations, the reference listed drug (Pediapred - 6.7mg/5mL PSP), and Prelone, an approved 15mg/5mL prednisolone product. All products were dosed to provide 15mg of prednisolone. The data clearly demonstrate the bioequivalence of the various products to each other. The study also demonstrates the lack of effect from the formulation differences among the products as suggested in the Agency's letter. Our response also addresses point #1 of the Agency's letter concerning the levels of certain ingredients in our formulation relative to the Agency's inactive ingredient guide. We trust that these data and information will adequately address the Agency concerns.

This represents a response to the second of the Agency's MAJOR bioequivalence deficiency letters (1/2/98 and 7/7/98). In each case new issues have been raised by the Agency and our responses have fully addressed the points included in the Agency's letters. Each response has required at least 6 months of Agency queue/review time. We also have responded to a MAJOR chemistry deficiency letter (11/26/97). That response was dated 4/28/98 and is

RECEIVED
SEP 24 1998
GENERIC DRUGS

presumably in the queue for review. With the significant review of our application that has occurred to date we believe it is reasonable to expect that all approval requirements have formally been identified to us in the Agency's letters of 11/26/97, 1/2/98, and 7/7/98. If there are any approval requirements that have not yet been identified to us in the FDA communications identified here, we request that these be communicated to us as soon as possible.

As always we appreciate the efforts expended by Agency personnel in our behalf. Please call if there are any questions, comments, or concerns related to this submission or our application.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory Affairs

2.1

JUL 7 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-117 APPLICANT: Ascent Pediatrics, Inc.

DRUG PRODUCT: Prednisolone Sodium Phosphate Oral Solution
(15 mg Prednisolone /5 mL)

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The test formulation contains certain inactive ingredients which either are not included in the approved drug products (maltitol), or whose concentrations in the proposed product exceed that found in drug product approved for the same dosage form and route of administration (sodium benzoate, monoammonium glycyrrhizinate, and fructose).

2. The Division is unable to conclude that differences in inactive ingredients discussed above will not significantly affect the absorption of the active moiety, prednisolone [Per 21 CFR 320.22(b)(3)(iii)].

   The argument made by the firm in reference to its application (ANDA is immaterial because the active ingredient is totally different.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-117 APPLICANT: Ascent Pediatrics, Inc.

DRUG PRODUCT: Prednisolone Sodium Phosphate Oral Solution
(15 mg Prednisolone /5 mL)

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The test formulation contains certain inactive ingredients which either are not included in the approved drug products (maltitol), or whose concentrations in the proposed product exceed that found in drug product approved for the same dosage form and route of administration (sodium benzoate, monoammonium glycyrrhizinate, and fructose).

2. The Division is unable to conclude that differences in inactive ingredients discussed above will not significantly affect the absorption of the active moiety, prednisolone [Per 21 CFR 320.22(b)(3)(iii)].

   The argument made by the firm in reference to its application (ANDA is immaterial because the active ingredient is totally different.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ASCENT PEDIATRICS, INC.

187 Ballardvale Street • Suite B125 • Wilmington, MA 01887 • Phone 978-658-2500 • Fax 978-658-3939

2/3/98

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD-600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockvile MD 20855-2773

ORIG AMENDMENT
N/AB

ANDA# 75-117
Prednisolone Sodium Phosphate Oral Solution 15mg/5mL
Bioequivalence Deficiency Response

Dear Mr. Sporn:

Reference is made to our ANDA# 75-117 for Prednisolone Sodium Phosphate Oral Solution 15mg/5mL and to the Agency's letter of 1/2/98.

Attached are full responses to all of the issues raised in the Agency's letter. We are providing information addressing the safety of the formulation components and use level cited by the reviewer. We strongly disagree with the bioequivalence reviewer's interpretation of 21CFR314.127(a)(8)(ii)(A)(2) and 21CFR314.127(a)(8)(ii)(A)(6) as stated in points 2 and 3 of the Agency's letter. A common reading of these regulations provides no language that precludes or prohibits the Agency from approving an ANDA for a product intended for oral administration strictly on the basis of a difference in formulation with regard to the reference listed drug. Outside counsel have confirmed our interpretation of these regulations. We request the reviewer reconsider his/her position on this point. Further, we point out that the Agency's Interim Inactive Ingredient Policy provides for differences in oral product formulations. The cited regulations do allow and provide the basis for non-approval if on the basis of information available to the Agency, there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed formulation raises serious questions of safety. We do not believe there is any basis for safety concerns with our formulation. The information contained in our responses support our position. We trust this information will adequately satisfy the reviewers concerns.

Please contact me by phone (978-658-2500) or fax (978-658-3939) should there be any additional questions related to the application.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory Affairs

RECEIVED
FEB 0 4 1998
GENERIC DRUGS

JAN 2 1998

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-117 APPLICANT: Ascent Pediatrics, Inc.

DRUG PRODUCT: Prednisolone Sodium Phosphate Oral Solution, 15mg/5ml

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. The formulation of the test product differs greatly from that of the reference listed drug.

2.

3.

4. The exact amount of fructose present in the test formulation is not reported.

5. The physical and chemical properties of the test product are not reported.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-117 APPLICANT: Ascent Pediatrics, Inc.

DRUG PRODUCT: Prednisolone Sodium Phosphate Oral Solution, 15mg/5ml

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. The formulation of the test product differs greatly from that of the reference listed drug.

2.

3.

4. The exact amount of fructose present in the test formulation is not reported.

5. The physical and chemical properties of the test product are not reported.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street • Suite B125 • Wilmington, MA 01887 • Phone 508-658-2500 • Fax 508-658-3939

April 21, 1997

P Greenberg 5/19/97

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

Re: ANDA Submission persuant to §505(j)(2)(c)

Orapred™ Solution, 15 mg prednisolone equivalent per 5 mL (prednisolone sodium phosphate oral solution)

The enclosed ANDA is submitted in under the provisions of §505(j)(2)(c) of the Act, based on an approved ANDA Suitability Petition for the new strength. Included are an archival copy in two volumes a and review copy in three volumes, as well as two extra bound copies of the Analytical Methods and Validation Package. A Field Copy, which Ascent certifies is a true copy of the CMC section, is being concurrently provided to the Boston District Office.

This application is for the approval of a new concentration (15 mg prednisolone equivalent per 5 mL) which differs from that of the Reference Listed Drug (RLD).

Labeling for the proposed new product is identical to that for the RLD, except for changes necessary to reflect formulation differences and manufacturer/ distributor. The proposed package insert also differs from that of the RLD in that it includes reference to two strengths--5 mg and 15 mg prednisolone equivalent per 5 mL. The 5 mg strength is being submitted concurrently as a separate ANDA application. It is proposed that both strengths would employ the same package insert. The container labels are designed to highlight the respective strengths in order to minimize the likelihood of pharmacy dispensing errors.

Since both the RLD and proposed new product are oral solutions, the application includes a request for waiver of the requirement for *in vivo* bioequivalence testing.

The proposed manufacturing and packaging records include a batch size intended for packaging into either 8 oz trade bottles or ½ oz sample bottles, and batch size intended for packaging into ½ oz sample bottles.

The products would be produced and released for Ascent by
Testing of raw materials and finished products would be handled by third-party laboratories, with results provided Ascent's QCU would provide appropriate oversight of these activities and would conduct its own independent audits as necessary.

ASCENT
PEDIATRICS, INC.

Should there be any questions, please feel free to contact me.

Yours truly,
ASCENT PEDIATRICS, INC.

Robert W. Mendes, Ph. D.
Vice President, Regulatory Affairs