

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 89-081

BIOEQUIVALENCE REVIEW(S)

Mr mgl 7/8/85

Greg

**MURO
PHARMACEUTICAL, INC.**

890 EAST STREET
TEWKSBURY, MASSACHUSETTS 01876
(617) 851-5981
1-800-225-0974

RE: NDA 89-081

June 21, 1985

Marvin Seife, M.D.
Director, Division of Generic Drugs
Room 16-170 HFN 230
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RESUBMISSION

ANDA ORIG AMENDMENT

BIOAVAILABILITY MATERIAL

Dear Dr. Seife:

Reference is made to your letters of March 19 and June 11, 1985 concerning application deficiencies relative to bioequivalency requirements.

On April 16, 1985 George D. Behrakis, President of Muro and I met with Dr. Dighe and Dr. Ise of the Division of Bioequivalence to discuss the listed deficiencies. The ANDA requirements for two dosage forms of prednisolone were discussed; tablets with no in-vivo bioequivalence requirements and an oral solution (Prelone) with an in-vivo bioequivalent requirement as per citizens petition Docket number 83P-0419/CP, Dec. 17, 1984.

A final agreement was reached for Muro to submit the data for our original study in accord with your March 19, 1985 letter, items 2-4.

Recognizing the Division's intention to propose that in-vivo bioequivalence testing not be required for ANDA approval of certain oral solutions as Prelone, we would have considered submission of a waiver from further in-vivo requirements. However, as agreed and to avoid further approval delays, statistical analysis of the data of our original study was performed by ^{data} presented here will remove deficiencies as outlined in your March 19, 1985 letter.

I trust you will find all information complete and in order so that we may obtain a speedy approval of our Prednisolone syrup.

Sincerely,

Joseph A. Celona
Joseph A. Celona
Director Quality Assurance

*For Complete
Study data
See Vol 1/2*

RECEIVED

JUN 24 1985

GENERIC DRUGS

Encls: Complete Bioavailability Study

JAC/cg

ANDA 89-001

Huro Pharmaceutical, Inc.
Attention: Joseph A. Celona
890 East Street
Tewksbury, MA 01876

DEC 13 1985

Gentlemen:

Reference is made to the bioavailability study amendment you submitted June 21, 1985 for Prednisolone Oral Solution 15 mg/5 mg.

The study amendment has been reviewed by our Division of Bioequivalence and they have the following comments:

1. All deficiencies identified in a previous review have been addressed.
2. The C_{max} and AUC ratios corrected for dose were incorrectly calculated by the firm. The correct ratios appear in this review (Table 3). The error does not affect any conclusions.
3. In all future submissions the firm must include the following:
 - a. Approval of the protocol by an investigational review board (IRB) prior to study initiation. A copy of the letter of approval must be submitted.
 - b. The test product must be a production lot or a lot produced on production equipment.
 - c. The screening laboratory results (blood chemistry), hematology, urinalysis) and medical histories for each subject must be included.
 - d. The qualifications of the principal investigator and co-investigators must be indicated (e.g. a curriculum vitae).

Recommendations:

1. Muro Pharmaceutical has conducted a bioavailability study comparing its PreloneTM (Prednisolone Syrup 15 mg/5 ml), Lot P04045L with its Liquid Pred^R (Prednisone Syrup 5 mg/5 ml, lot P05045L. Presently, there are no approved liquid formulations of prednisolone on the market. Prednisone liquid is an appropriate reference formulation since prednisone is quickly converted in-vivo to prednisolone. In fact, most evaluations of prednisone pharmacokinetics are in terms of prednisolone. The Division of Bioequivalence has found Muro Pharmaceutical's bioavailability study acceptable. The study demonstrates Muro Pharmaceutical's PreloneTM (Prednisolone Syrup 15 mg/5 ml) has superior bioavailability as compared to the reference product, Muro Pharmaceutical's Liquid Pred^R (Prednisone Syrup 5 mg/5 ml).
2. Please disregard our letter of November 4, 1985 in which we mistakenly reiterated the deficiencies from our March 19, 1985 letter. You have satisfactorily responded to the deficiencies enumerated in that letter."

Sincerely yours,

✓ 12-13-85
Harvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 12/10/85
FROM: Director, Division of Bioequivalence MFN-250		OFFICE
TO: Director, Division of Generic Drugs		DIVISION MFN-230
SUBJECT: Prednisolone (Prelone) Syrup, 15mg/5ml; Muro		
SUMMARY: Pharmaceuticals, ANDA # 89-081.		
<p>Muro Pharmaceuticals filed its ANDA for Prednisolone Syrup, 15mg/5ml prior to the enactment of Drug Price Competition and Patent Extension Act of 1984. Muro was advised, in January of 1984, to conduct a <u>bioavailability</u> study to demonstrate that the syrup product is bioavailable. The firm was told, at that time, to compare the bioavailability of its syrup product with its prednisone liquid (5mg/5ml). The firm conducted the study as advised, and submitted it on Nov. 20, 1984.</p> <p>This study is not, and is not meant to be a bioequivalence study. There is no approved prednisolone syrup on the market, and this is the first syrup product of prednisolone. A bioavailability study would, therefore, suffice. Dr. Fiske of the Division of Bioequivalence found the study acceptable recently. From the biopharmaceutics point of view the applicant is approvable.</p>		
51	12/10/85	DOCUMENT NUMBER

249
OCT 16 1985

-Prednisolone (Prelone)
15 mg/5 ml Syrup
ANDA #89-081
Reviewer: William D. Fiske
Wang #5895e

Muro Pharmaceutical, Inc.
Tewksbury, MA
Submission Dates:
November 20, 1984
June 21, 1985

REVIEW OF AN AMENDMENT TO A BIOAVAILABILITY STUDY

The latest submission is an amendment to the bioavailability study submitted on 11/20/84. The review of the study by the Division of Bioequivalence was completed on 3/12/85 with the recommendation that the study was unacceptable due to four deficiencies. The Division of Generic Drugs informed the firm of the 4 deficiencies in a letter dated 3/19/85. The amendment (6/21/85) cover letter describes a meeting taking place between George D. Behrakis, President and Joseph A. Calona, Director of Quality Assurance, both from Muro, and Drs. Dighe and Ise from the FDA, Division of Bioequivalence. The meeting took place on April 16, 1985 and it was agreed Muro would submit data in accord with items 2 - 4 in the FDA's 3/19/85 letter to the firm.

Since the study has been previously reviewed, only the deficiencies will be reviewed and data summarized. A copy of the previous review is attached as Appendix 1. The deficiencies in the 3/19/85 letter correspond to the reviewer's comments 1 - 4. Only 2 - 4 needed to be addressed.

Deficiency 2 Correction:

The firm has now provided sufficient assay validation. Mean percent analytical recovery was 4% for the range of interest. Percent extraction recovery for 50 ng/ml and 400 ng/ml spiked samples was 100% and 100% respectively. Within and between run reproducibility was very good with coefficients of variation of 10% for the spiked samples. Linearity was demonstrated from 10 - 750 ng/ml. Sensitivity was adequate down to 10 ng/ml. Specificity was shown and lack of interference from cortisone, cortisol, methylprednisolone, methylprednisone and 6 β -hydroxycortisol, a metabolite.

With the validation the firm also supplied all the subjects' data which supported all aspects of the assay validation.

Deficiency 3 Correction:

The firm supplied complete ANOVA tables for all parameters required and a summary table is included in this review (Table 1). Power calculations were not performed, but from the ANOVA tables I calculated the power of the test for C_{max} and AUC_{0- ∞} . The firm correctly indicated that the SAS GLM analysis in this instance is not necessary.

Deficiency 4 Correction:

Comment 4 is actually a caution to the firm; an affirmation of the appropriate use of dose correction; and a statement that only AUC, C_{max} and T_{max} values, with statistical analysis are needed.

Summary:

A two-way crossover study in 6 subjects of oral liquid formulations of prednisone and prednisolone was performed. Comparison of the parameters obtained from the serum concentration-time profiles of prednisolone in the subjects was performed. The comparison of the parameters with respect to solution administered and statistical analysis is in Table 1. Mean serum concentrations of prednisolone versus time for both solutions are presented in Table 2. In Table 3 are the C_{max} and AUC ratios for each subject.

Comments:

1. The bioavailability study demonstrates prednisolone liquid produces serum levels of prednisolone superior to those produced by prednisone liquid. Measures of bioavailability, C_{max} and AUC, were significantly higher after administration of prednisolone. C_{max} was 29% greater and AUC was 24% greater. The time to peak concentration, T_{max} was similar (0.54 versus 0.63 hours).
2. All deficiencies identified in a previous review (Appendix 1) have been addressed.
3. The C_{max} and AUC ratios corrected for dose were incorrectly calculated by the firm. The correct ratios appear in this review (Table 3). The error does not affect any conclusions.

Comment 4 is not to be released under the Freedom of Information Act.

Recommendations:

1. Muro Pharmaceutical has conducted a bioavailability study comparing its Prelone™ (Prednisolone Syrup 15 mg/5 ml), Lot P04045L with its Liquid Pred^R (Prednisone Syrup 5 mg/5 ml), lot P06045L. Presently, there are no approved liquid formulations of prednisolone on the market. Prednisone liquid is an appropriate reference formulation since prednisone is quickly converted in-vivo to prednisolone. In fact, most evaluations of prednisone pharmacokinetics are in terms of prednisolone. The Division of Bioequivalence has found Muro Pharmaceutical's bioavailability study acceptable. The study demonstrates Muro Pharmaceutical's Prelone™ (Prednisolone Syrup 15 mg/5 ml) has superior bioavailability as compared to the reference product, Muro Pharmaceutical's Liquid Pred^R (Prednisone Syrup 5 mg/5 ml).

The firm should be informed of comments 2, 3 and 4, and the above recommendation.

REVIEW SECTION

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Table 1

Mean pharmacokinetic parameters obtained from
6 subjects after administration of prednisolone
liquid (15 mg) or prednisone liquid (15 mg)

<u>Parameter</u>	<u>Prednisolone</u>	<u>Prednisone^a</u>	<u>p value</u>
C _{max} (ng/ml)	430.3 (14.5) ^b <i>OK</i>	333.0 (8.3) <i>OK</i>	<0.05
T _{max} (hr)	0.54 (18.5)	0.63 (22.2)	ND
AUC _T (ng x hr/ml) <i>OK</i>	2024 (12.0)	1632 (13.8)	<0.05
K _a (hr ⁻¹) <i>OK</i>	0.685 (21.9)	0.836 (41.0)	NS
K _{overall elim.} (hr ⁻¹) <i>OK</i>	0.244 (9.8)	0.245 (16.8)	NS
Cl _T corr ^c (ml/min-1.73m ²) <i>OK</i>	127.2 (11.1)	149.3 (12.0)	<0.05

a) All parameters were obtained from serum prednisolone concentrations.

b) Values in () are percent coefficient of variation.

c) Corr refers to correction for administered dose.
Correction factor = 108/101 = 1.069.

OK

Table 2

Mean serum concentrations of prednisolone versus time
in 6 subjects after administration of liquid prednisolone
(15 mg) or liquid prednisone (15 mg).
Percent coefficient of variation is in ().

<u>Time (hr)</u>	<u>Prednisolone (ng/ml)</u>	<u>Prednisone (ng/ml)</u>
0	0	0
0.25	307 (37) ^{ok}	243 (25) ^{ok}
0.5	425 (16)	317 (11)
0.75	369 (8)	313 (9)
1.0	341 (7)	279 (5)
1.25	332 (11)	272 (6)
1.5	302 (8)	254 (7)
1.75	308 (6)	250 (10)
2.0	298 (11)	238 (7)
3.0	250 (8)	197 (8)
4.0	199 (8)	160 (12)
6.0	135 (13)	109 (14)
8.0	79 (20)	63 (23)
10.0	53 (28)	40 (31)
12.0	31 (26)	26 (40)

Table 3

Individual ratios for AUC and Cmax in
subjects administered liquid prednisolone
(15 mg) or liquid prednisone (15 mg).

<u>Subject</u>	<u>AUC (ng x hr/ml)</u> <i>OK</i>			<u>Cmax (ng/ml)</u> <i>OK</i>		
	<u>Test Ref.</u>	<u>Ratio</u>	<u>Corr Ratio</u>	<u>Test Ref.</u>	<u>Ratio</u>	<u>Corr Ratio</u>
1	1962 1579	1.24	1.16	436 354	1.23	1.15
2	2408 2053	1.17	1.09	470 319	1.47	1.38
3	1876 1668	1.12	1.05	401 356	1.13	1.06
4	1920 1576	1.22	1.14	401 353	1.13	1.06
5	1759 1395	1.26	1.18	347 285	1.22	1.14
6	2222 1521	1.46	1.37	527 330	1.59	1.49
0.75 - 1.25 pass/total		4/6	5/6		4/6	4/6

corr = 101/108 = 1.069 *OK*

MAR 12 1985

Prednisolone (Prelone)
15 mg/5 ml Solution
ANDA # 89-081
Reviewer: A. Jackson
Wang # 4882e

Muro Pharmaceutical
Tewksbury, MA
Submission Date:
November 20, 1984

Review of Bioavailability Study

Objective:

The study was designed to evaluate the absorption characteristics and bioavailability of a new liquid prednisolone preparation.

Materials and Methods:

Prednisolone pharmacokinetics were evaluated in six subjects using two liquid formulations. The reference formulation was prednisone liquid (5 mg/5 ml) - Muro Pharmaceutical lot # P06045L while the test drug was prednisone liquid 15 mg/5 ml Muro Pharmaceutical lot # P04045L.

Clinical:

The study was done at the _____ under the clinical direction of _____ M.D. and _____
The study was done in six healthy adult males between 27 and 41 years of age. Their weights ranged from 64.5 to 78.5 kg and did not vary by more than $\pm 10\%$ from normal for height and age.

Criteria for study enrollment included a physical examination within 30 days of initiation of the study. This examination included a medical history, hemogram (hemoglobin, hematocrit), urinalysis (including microscopic analysis), biochemical profile (blood urea nitrogen, serum alkaline phosphatase, SGOT, serum bilirubin, albumin, total protein) and a guaiac paper test for fecal occult blood. Exclusions from the study included abnormalities of any of the above studies, a history of chronic alcohol consumption, gastrointestinal or cardiovascular disease, tuberculosis, the presence or history of chronic infection or psychosis. Subjects were also excluded if they had received any corticosteroid medication within 30 days of the study or any other medication for a period of seven days prior to or during the test period.

The study was done as a two way crossover separated by a one week washout period. Each study day was preceded by a ten-hour fast which continued until four hours after the study medication was administered. The study dose was given in a cup which was then washed twice using the eight ounces of water given with the study medication. To assure proper stomach emptying, subjects were not permitted to lie down for the first two hours after administration of the study medication. Strenuous exercise was also prohibited on the day of the study. Venous blood samples were obtained via an intravenous catheter at times 0, 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0 and 12.0 hours. blood samples were separated the same day. Plasma was then stored at -0.20°C until analysis.

Analytical:

The samples were assayed by high performance liquid chromatography using a method published by Rose and Jusko, J.Chromatogr 162:273-280, 1979.

Data Analysis:

Pharmacokinetic parameters for prednisolone were determined assuming first order kinetics. Peak plasma concentrations and time of peak concentration were obtained from the plasma prednisolone concentration vs time curve. The total area under the plasma concentration vs time curve (AUC) was calculated using the trapezoidal rule. The AUC beyond the last plasma steroid concentration obtained was calculated by dividing the last measured plasma prednisolone concentration by the elimination rate constant (λ_2). The elimination rate constant was calculated using a nonlinear least squares fit of the logarithmic plasma concentration-time plot.

Comments:

1. The Division of Bioequivalence seriously doubts that a study with only 6 subjects would have sufficient power, therefore the current study can be considered as only a pilot investigation to obtain an estimate of the number of subjects required to do a complete study.
2. The firm must submit a complete assay validation including standard and subject chromatograms, including within and between day variation and assay sensitivity at a defined signal to noise ratio.
3. The complete ANOVA table and all power calculations must be submitted with the final application. Also include a comparison of treatment means in the SAS GLM analysis.
4. The Division of Bioequivalence would like to caution the firm against making all of the corrections in estimating F (Fraction Absorbed) because several assumptions are being made that may be difficult to substantiate. The company should be advised that corrections for administered dose are appropriate and that a statistical comparison of AUC, C_{max} , T_{max} and individual plasma concentrations are the only requirements required for bioequivalency.

Recommendation:

The bioavailability study conducted by Muro Pharmaceutical on its 15 mg solution of prednisolone Lot # P04045L, comparing it to Muro Prelone 5mg/5 ml is unacceptable to the Division of Bioequivalence because of the deficiencies cited under comments 1-4.

The firm should be informed of the deficiencies.

INDA 89-081

Muro Pharmaceutical Inc.
Attention: Joseph A Celona
890 East Street
Tewksbury, MA 01876

Gentlemen:

Reference is made to the bioavailability study amendment you submitted on June 21, 1985 for Prednisolone Oral Solution 15 mg/5 ml.

The study has been reviewed by our Division of Bioequivalence and they have the following comments:

1. The Division of Bioequivalence seriously doubts that a study with only 6 subjects would have sufficient power, therefore the current study can be considered as only a pilot investigation to obtain an estimate of the number of subjects required to do a complete study.
2. The firm must submit a complete assay validation including standard and subject chromatograms, including within and between day variation and assay sensitivity at a defined signal to noise ratio.
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Recommendation:

The bioavailability study conducted by Muro Pharmaceutical on its 15 mg solution of Prednisolone Lot # P04045L, comparing it to Muro Predlone 5 mg/5 ml is unacceptable to the Division of Bioequivalence because of the deficiencies cited under comments 1-4."

Sincerely yours,

:/10-31-85

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

FOR

11-4-85

Disregard this letter. Letter enumerates deficiencies which were earlier cited & relayed to the firm.

NDA 89-081

Huro Pharmaceuticals, Inc.
Attention: Joseph A. Celona
890 East Street
Tewksbury, MA 01876

JUN 11 1985

Gentlemen:

Please refer to your abbreviated new drug application dated November 20, 1984, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the preparation Prelone (Prednisolone) Oral Solution 15 mg/5 ml.

Reference is also made to your communication dated May 28, 1985 and our letter dated March 19, 1985. *Bio letter*

The application is deficient and therefore not approvable under Section 505(j)(3) of the Act as follows:

Please reply to our letter referenced above.

The file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.110(d). If you do so, the application shall be re-evaluated and within 90 days of the date of receipt of such request (or additional period as we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours, *A*

7/10/85
r/MSeif Harvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics
procl/cls

MAR 19 1985

NDA 89-081

Muro Pharmaceutical, Inc.
Attention: Joseph A. Celona
890 East Street
Tewksbury, MA 01876

Gentlemen:

Reference is made to the bioavailability study you submitted on November 20, 1984, for Prelone (Prednisolone) Oral Solution 15 mg/5ml.

The study has been reviewed by our Division of Bioequivalence and they have the following comments:

1. The Division of Bioequivalence seriously doubts that a study with only 6 subjects would have sufficient power; therefore, the current study can be considered as only a pilot investigation to obtain an estimate of the number of subjects required to do a complete study.
2. The firm must submit a complete assay validation including standard and subject chromatograms, including within and between day variation and assay sensitivity at a defined signal to noise ratio.
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Recommendation:

The bioavailability study conducted by Muro Pharmaceutical on its 15 mg solution of prednisolone Lot # P04045L, comparing it to Muro Prelone 5 mg/5 ml is unacceptable to the Division of Bioequivalence because of the deficiencies cited under comments 1-4."

Sincerely yours,

3/19/85
MARK D. Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

1/8/85

MAR 12 1985

Prednisolone (Prelone)
15 mg/5 ml Solution
ANDA # 89-081
Reviewer: A. Jackson
Wang # 4882e

Muro Pharmaceutical
Tewksbury, MA
Submission Date:
November 20, 1984

Review of Bioavailability Study

Objective:

The study was designed to evaluate the absorption characteristics and bioavailability of a new liquid prednisolone preparation.

Materials and Methods:

Prednisolone pharmacokinetics were evaluated in six subjects using two liquid formulations. The reference formulation was prednisone liquid (5 mg/5 ml) Muro Pharmaceutical lot # P06045L while the test drug was prednisone liquid 15 mg/5 ml Muro Pharmaceutical lot # P04045L.

Clinical:

The study was done at the Denver, Colorado, under the clinical direction of [redacted] and [redacted]. The study was done in six healthy adult males between 27 and 41 years of age. Their weights ranged from 64.5 to 78.5 kg and did not vary by more than $\pm 10\%$ from normal for height and age.

Criteria for study enrollment included a physical examination within 30 days of initiation of the study. This examination included a medical history, hemogram (hemoglobin, hematocrit), urinalysis (including microscopic analysis), biochemical profile (blood urea nitrogen, serum alkaline phosphatase, SGOT, serum bilirubin, albumin, total protein) and a guaiac paper test for fecal occult blood. Exclusions from the study included abnormalities of any of the above studies, a history of chronic alcohol consumption, gastrointestinal or cardiovascular disease, tuberculosis, the presence or history of chronic infection or psychosis. Subjects were also excluded if they had received any corticosteroid medication within 30 days of the study or any other medication for a period of seven days prior to or during the test period.

The study was done as a two way crossover separated by a one week washout period. Each study day was preceded by a ten-hour fast which continued until four hours after the study medication was administered. The study dose was given in a cup which was then washed twice using the eight ounces of water given with the study medication. To assure proper stomach emptying, subjects were not permitted to lie down for the first two hours after administration of the study medication. Strenuous exercise was also prohibited on the day of the study. Venous blood samples were obtained via an intravenous catheter at times 0, 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0 and 12.0 hours. blood samples were separated the same day. Plasma was then stored at -0.20°C until analysis.

Analytical:

The samples were assayed by high performance liquid chromatography using a method published by Rose and Jusko, J.Chromatogr 162:273-280, 1979.

Data Analysis:

Pharmacokinetic parameters for prednisolone were determined assuming first order kinetics. Peak plasma concentrations and time of peak concentration were obtained from the plasma prednisolone concentration vs time curve. The total area under the plasma concentration vs time curve (AUC) was calculated using the trapezoidal rule. The AUC beyond the last plasma steroid concentration obtained was calculated by dividing the last measured plasma prednisolone concentration by the elimination rate constant (λ_2). The elimination rate constant was calculated using a nonlinear least squares fit of the logarithmic plasma concentration-time plot.

Comments:

1. The Division of Bioequivalence seriously doubts that a study with only 6 subjects would have sufficient power, therefore the current study can be considered as only a pilot investigation to obtain an estimate of the number of subjects required to do a complete study.
2. The firm must submit a complete assay validation including standard and subject chromatograms, including within and between day variation and assay sensitivity at a defined signal to noise ratio.
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Recommendation:

The bioavailability study conducted by Muro Pharmaceutical on its 15 mg solution of prednisolone Lot # P04045L, comparing it to Muro Prelone 5mg/5 ml is unacceptable to the Division of Bioequivalence because of the deficiencies cited under comments 1-4.

The firm should be informed of the deficiencies.

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MAR 12 1985

Prednisolone (Prelone)
15 mg/5 ml Solution
ANDA # 89-081
Reviewer: A. Jackson
Wang # 4882e

Muro Pharmaceutical
Tewksbury, MA
Submission Date:
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Clinical:

The study was done at the Denver, Colorado site under the clinical direction of Dr. [redacted] and Dr. [redacted]. The study was done in six healthy adult males between 27 and 41 years of age. Their weights ranged from 64.5 to 78.5 kg and did not vary by more than $\pm 10\%$ from normal for height and age.

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The study was done as a two way crossover separated by a one week washout period. Each study day was preceded by a ten-hour fast which continued until four hours after the study medication was administered. The study dose was given in a cup which was then washed twice using the eight ounces of water given with the study medication. To assure proper stomach emptying, subjects were not permitted to lie down for the first two hours after administration of the study medication. Strenuous exercise was also prohibited on the day of the study. Venous blood samples were obtained via an intravenous catheter at times 0, 0.25, 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0 and 12.0 hours. blood samples were separated the same day. Plasma was then stored at -0.20°C until analysis.

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Comments:

1. The Division of Bioequivalence seriously doubts that a study with only 6 subjects would have sufficient power, therefore the current study can be considered as only a pilot investigation to obtain an estimate of the number of subjects required to do a complete study.
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Recommendation:

The bioavailability study conducted by Muro Pharmaceutical on its 15 mg solution of prednisolone Lot # P04045L, comparing it to Muro Prelone 5mg/5 ml is unacceptable to the Division of Bioequivalence because of the deficiencies cited under comments 1-4.

The firm should be informed of the deficiencies.

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