CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 79-113

Name: Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/ 38 mg (OTC)

Sponsor: Perrigo R&D Company

Approval Date: December 22, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-113

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-113

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 79-113

Perrigo R&D Company
Attention: Valerie Gallagher
Associate Director, Regulatory Affairs
515 Eastern Avenue
Allegan, MI 49010

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated August 17, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg (OTC).

Reference is also made to the Tentative Approval letter issued by this office on October 27, 2008, and to your amendments dated February 13, March 27, October 24, and November 7, 2008.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for over-the-counter (OTC) use as recommended in the submitted labeling. Accordingly, the ANDA is approved effective on the date of this letter. The Division of Bioequivalence has determined your Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg to be bioequivalent to the reference listed drug, Advil PM Tablets, 200 mg/38 mg, of Wyeth Consumer Healthcare. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as "***Miscellaneous Correspondence - SPL for Approved ANDA 79-113***".

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert L. West
12/22/2008 03:54:13 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-113

TENTATIVE APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 79-113

Perrigo R&D Company
Attention: Valerie Gallagher
Associate Director, Regulatory Affairs
515 Eastern Avenue
Allegan, MI 49010

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated August 17, 2007 submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg.

Reference is also made to your amendments dated March 27, June 3, June 11, July 7, July 22, July 24, and October 24, 2008.

We have completed the review of this ANDA and based upon the information you have presented to date, we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the exclusivity issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time, (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug (RLD) upon which you have based your ANDA, Advil PM, 200 mg/38 mg, of Wyeth Consumer Healthcare, is subject to a period of exclusivity as noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), which expires December 21, 2008.

With respect to the exclusivity granted to Wyeth and expiring on December 21, 2008, you state that you are not seeking approval until such time the exclusivity period expires.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. Any data pertaining to the new USP requirements for assessing (b) (4) should also be included. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendments requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book." Should you believe that there are

grounds for issuing the final approval letter prior to, you should amend your ANDA accordingly.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Dat Doan, Project Manager, at 240-276-8573.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gary Buehler

10/27/2008 10:49:20 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-113

LABELING

20 Count Bottle Label
Final Printed Labeling

(b) (4)

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)/Nighttime Sleep-Aid

20 Coated **CAPLETS****

***CAPSULE-SHAPED TABLETS*

READ AND KEEP CARTON FOR COMPLETE WARNINGS AND INFORMATION

Uses ■ for relief of occasional sleeplessness when associated wi h minor aches and pains ■ helps you fall asleep and stay asleep

Warnings

■ **ask your doctor before use** if you are pregnant, under a doctor's care for any continuing medical illness, age 60 or over, taking any other drug or have stomach problems ■ this product may cause a **severe allergic reaction,** especially in people a lergic to aspirin. Symptoms may include: hives, facial swe ling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away. ■ **do not use** this product if you have ever had an a lergic reaction to any pain reliever fever reducer; unless you have time for a full night's sleep; in ch ldren under 12 years or with any other product containing diphenhydramine ■ this product may cause **stomach bleeding** ■ **when using this product** drowsiness wi l occur. Do not drive a motor vehicle or operate machinery. Avoid alcoholic drinks. ■ **long term continuous use** may increase the risk of heart attack or stroke

Directions

■ **do not take more than directed** ■ do not take longer than 10 days, unless directed by a doctor ■ adults and ch ldren 12 years and over: take 2 caplets at bedtime ■ do not take more than 2 caplets in 24 hours Store at 20-25°C (68-77°F). Avoid excessive heat above 40°C (104°F).

Questions or comments? **1-800-719-9260**

Do not use if printed foil under cap is broken or missing

D STRIBUTED BY

PERRIGO®

ALLEGAN MI 49010

CODE AREA

(b) (4)

: 05060 FA F2

TO ARTIST:

(b) (4)

FORMAT: MODIFIED

TYPE SIZES:

HEADINGS: (b) (4)

SUBHEADINGS (b) (4)

TEXT: (b) (4)

LEADING: (b) (4)

BULLETS (b) (4)

LINE USED (b)

STATEMENT INSIDE BOX (b) (4)

5-30-08

500 Count Bottle Label
Final Printed Labeling

(b) (4)

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

Pain Reliever (NSAID)/ Nighttime Sleep-Aid

500 Coated CAPLETS**

**CAPSULE-SHAPED TABLETS

Drug Facts

Active ingredients (in each caplet)	Purposes
Diphenhydramine citrate 38 mg	Nighttime sleep-aid
Ibuprofen 200 mg (NSAID)*	Pain reliever

*nonsteroidal anti-inflammatory drug

Uses
- for relief of occasional sleeplessness when associated with minor aches and pains
- helps you fall asleep and stay asleep

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:
- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if you:
- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing an NSAID [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use
- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- unless you have time for a full night's sleep
- in children under 12 years of age
- right before or after heart surgery
- with any other product containing diphenhydramine, even one used on skin
- if you have sleeplessness without pain

Ask a doctor before use if you have
- a breathing problem such as emphysema or chronic bronchitis
- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach or stomach pain
- ulcers
- bleeding problems
- high blood pressure
- heart or kidney disease
- asthma
- taken a diuretic
- reached age 60 or older
- glaucoma
- trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are
- taking sedatives or tranquilizers, or any other sleep-aid
- taking any other drug containing an NSAID (prescription or nonprescription)
- under a doctor's care for any continuing medical illness

Drug Facts (continued)

- taking any other antihistamines
- taking a blood thinning (anticoagulant) or steroid drug
- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product
- drowsiness will occur
- avoid alcoholic drinks
- do not drive a motor vehicle or operate machinery
- take with food or milk if stomach upset occurs
- long term continuous use may increase the risk of heart attack or stroke

Stop use and ask a doctor if
- you feel faint, vomit blood, or have bloody or black stools. These are signs of stomach bleeding.
- pain gets worse or lasts more than 10 days
- sleeplessness persists continuously for more than 2 weeks. Insomnia may be a symptom of a serious underlying medical illness.
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
- **do not take more than directed**
- do not take longer than 10 days, unless directed by a doctor (see Warnings)
- adults and children 12 years and over: take 2 caplets at bedtime
- do not take more than 2 caplets in 24 hours

Other information
- read all warnings and directions before use
- store at 20-25°C (68-77°F)
- avoid excessive heat above 40°C (104°F)

Inactive ingredients colloidal silicon dioxide, croscarmellose sodium, FD&C blue #2 aluminum lake, glyceryl behenate, hydroxypropyl cellulose, iron oxide black, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, pregelatinized starch, talc, titanium dioxide

Questions or comments? 1-800-719-9260

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0 00000 00000 0

DO NOT USE IF PRINTED FOIL UNDER CAP IS BROKEN OR MISSING

CODE AREA (b) (4)

: 05090 FA F3

TO ARTIST:

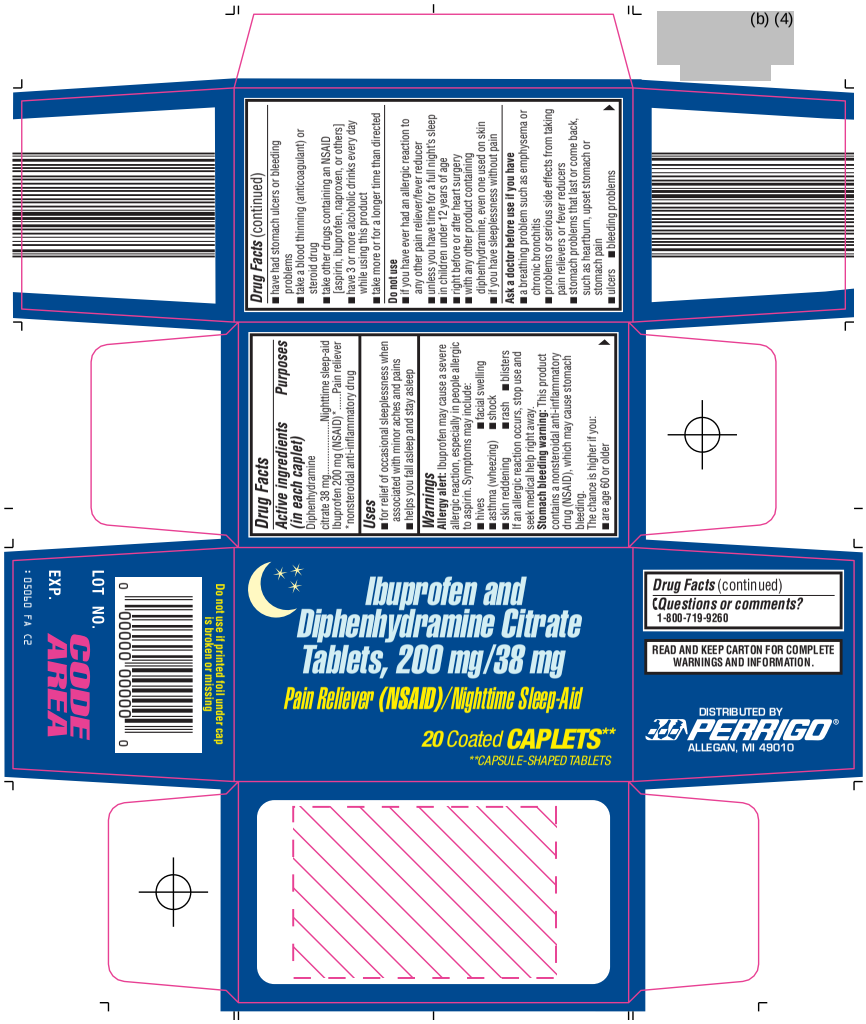
(b) (4)

FORMAT: MODIFIED

(b) (4)

7-2-08

20 Count Bottle Carton
Final Printed Labeling



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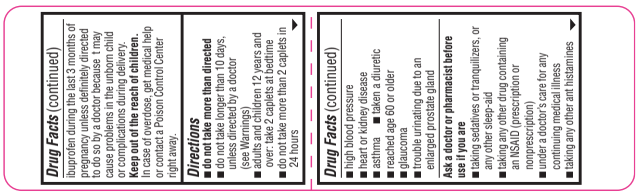
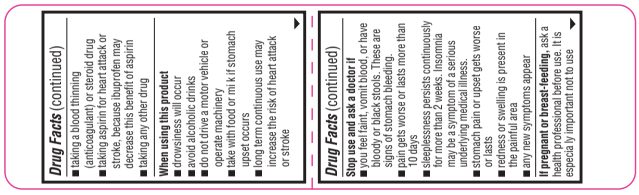


PANEL #4 PANEL #1



PANEL #2 PANEL #3

FORMAT: STANDARD

TYPE SIZES:

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TITLE (continued) (b) (4)
HEADINGS: (b) (4)
SUBHEADINGS: (b) (4)
TEXT (b) (4)
LEADING (b) (4)
BULLETS: (b) (4)
TELEPHONE #: (b) (4)
HEAVY LINES: (b)
HAIRLINES: (b)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-113

LABELING REVIEWS

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 79-113
Date of Submission: **June 3, 2008 and July 7, 2008**
Applicant's Name: Perrigo R&D Company
Established Name: Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

---

Approval Summary

1. **Do you have copies of final printed labels and labeling?** Yes

2. **CONTAINER – Bottles 20 and 500**
   Satisfactory in **final print** as of the July 7, 2008 electronic submission

3. CARTON – (20 count container only)
   Satisfactory in **final print** as of the July 7, 2008 electronic submission

4. **Patent Information: Firm filed paragraph III**

Patent Data: NDA 21-394

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	*None*	None	None	None	None

Exclusivity Data: NDA 21-394

Code	Reference	Expiration	Labeling Impact
NC	New Combination.	Dec. 21, 2008	None

5. **Revisions needed post-approval**; None

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Advil PM®
NDA Number: N 21-394
NDA Drug Name: Advil PM®
NDA Firm: N 21-394/S-010; Approved June 12, 2008
Date of Approval of NDA Insert and supplement: N 21-394/S-010; Approved June 12, 2008
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container: Most recently approved labeling of the reference listed drug, Advil PM®.

FOR THE RECORD:

1. Professional Package Insert:
   Model labeling used by the firm for Advil PM® was approved June 12, 2008; (N 21-394/S-010)

2. Storage/Dispensing Conditions:

NDA: Store at 20º-25ºC(68º-77ºF). Avoid excessive heat above 40°C (104°F).
ANDA: Store at 20-25°C (68-77°F). Avoid excessive heat above 40°C (104°F).

3. Product Line:
   RLD – 4, 20, 40 and 80 count container/carton
   ANDA – 20 count and 500 count bottles

4. Inactive Ingredients:
   The listing of the inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition statement.

Description and Composition of the Drug Product

What are the components and composition of the final product? What are the functions(s) of each excipient? See the following tables. **Satisfactory**.

The drug product consists of 200 mg Ibuprofen (IBU) and 38 mg Diphenhydramine Citrate (DPC) as active substances per tablet. The quantitative composition and function of each component in the drug product is listed in the table below.

Ingredient	Function	Weight mg/tablet	% (w/w)
Diphenhydramine Citrate, USP	Active Ingredient	38.0	(b) (4)
Ibuprofen, USP	Active Ingredient	200.0	
Colloidal Silicon Dioxide, NF	(b) (4)		
Croscarmellose Sodium, NF			
FD&C Blue #2			
Glyceryl Behenate, NF			
Hydroxypropylcellulose, NF			
Iron Oxide Black			
Lactose Monohydrate, NF			
Magnesium Stearate, NF			
Microcrystalline Cellulose, NF			
Polyethylene Glycol, USP			
Polyvinyl Alcohol, USP			
Pregelatinized Starch, NF			
(b) (4)			
Talc, USP			
Titanium Dioxide, USP			
Total Weight		(b) (4)	**100.00**

(b) (4)

5. Container/Closure: The proposed container/closure system is a (b) (4) and is commonly used for solid oral dosage forms. The proposed container/closure system has been qualified as safe for use with this dosage form.

MARKETED CONTAINER CLOSURE SYSTEMS

Container Closure System	Component	Component Number	Resin
20 Count	(b) (4) Bottle	(b) (4)	(b) (4)
	Cap	(b) (4)	
500 Count	(b) (4) Bottle	(b) (4)	
	Cap	(b) (4)	

6. All manufacturing will be performed by Perrigo Co.

Date of Review: 7/15/08 **Date of Submission: June 3, 2008 & July 7, 2008**
Primary Reviewer: J Barlow **Date:**

Team Leader: J Grace **Date:**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James Barlow
7/16/2008 03:38:52 PM
LABELING REVIEWER

John Grace
7/17/2008 10:30:47 AM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	79-113
Date of Submission:	August 17, 2007
Applicant's Name:	Perrigo R&D Company.
Established Name:	Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

---

Labeling Deficiencies:

1. **CONTAINER – Bottles 20 and 500**
   Front Panel: Revise to read as follows – Relocate the "20" and include "Coated"

   Ibuprofen, 200 mg/Diphenhydramine citrate, 38 mg Caplets**

   20 Coated **Capsule-shaped Tablets

2. **CARTON – (20 count container only)**
   Satisfactory in **final print** as of the August 17, 2007 electronic submission

(b) (4)

Submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

FOR THE RECORD:

1. Professional Package Insert:
   Model labeling used by the firm for Advil PM® was approved December 21, 2005; (N 21-394; approved December 21, 2005)

2. Storage/Dispensing Conditions:
   NDA: Store at 20º-25ºC(68º-77ºF). Avoid excessive heat above 40°C (104°F).
   ANDA: Store at 20-25°C (68-77°F). Avoid excessive heat above 40°C (104°F).

3. Product Line:
   RLD – 4, 20, 40 and 80 count container/carton
   ANDA – 20 count and 500 count bottles

4. Inactive Ingredients:
   The listing of the inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition statement.

Description and Composition of the Drug Product

What are the components and composition of the final product? What are the functions(s) of each excipient? See the following tables. **Satisfactory**.

The drug product consists of 200 mg Ibuprofen (IBU) and 38 mg Diphenhydramine Citrate (DPC) as active substances per tablet. The quantitative composition and function of each component in the drug product is listed in the table below.

Ingredient	Function	Weight mg/tablet	% (w/w)
Diphenhydramine Citrate, USP	Active Ingredient	38.0	(b) (4)
Ibuprofen, USP	Active Ingredient	200.0	
Colloidal Silicon Dioxide, NF		(b) (4)	
Croscarmellose Sodium, NF			
FD&C Blue #2			
Glyceryl Behenate, NF			
Hydroxypropylcellulose, NF			
Iron Oxide Black			
Lactose Monohydrate, NF			
Magnesium Stearate, NF			
Microcrystalline Cellulose, NF			
Polyethylene Glycol, USP			
Polyvinyl Alcohol, USP			
Pregelatinized Starch, NF			
(b) (4)			
Talc, USP			
Titanium Dioxide, USP			
Total Weight		(b) (4)	**100.00**

1 (b) (4)

5. Container/Closure: The proposed container/closure system is a (b) (4) and is commonly used for solid oral dosage forms. The proposed container/closure system has been qualified as safe for use with this dosage form.

MARKETED CONTAINER CLOSURE SYSTEMS

Container Closure System	Component	Component Number	Resin
20 Count	(b) (4) Bottle	(b) (4)	(b) (4)
	Cap	(b) (4)	
500 Count	(b) (4) Bottle	(b) (4)	
	Cap	(b) (4)	

6. All manufacturing will be performed by Perrigo Co.

Date of Review: 5/12/08 **Date of Submission: August 17, 2007**
Primary Reviewer: J Barlow **Date:**

Team Leader: J Grace **Date:**

cc: ANDA: 79-113
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSNZ\PERRIGO\LTRS&REV\79113notapprovablereview.labeling.doc
Review

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James Barlow
5/12/2008 04:53:55 PM
LABELING REVIEWER

John Grace
5/15/2008 11:39:08 AM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-113

CHEMISTRY REVIEWS

ANDA 79-113

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

Perrigo R & D Company

Yusuf Amin
OGD – Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 79-113

2. REVIEW #: 3

3. REVIEW DATE: 21-NOV-2008

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	17-AUG-2007
Amendment	03-DEC-2007
Amendment	27-MAR-2008
Amendment	11-JUN-2008
Amendment (withdrawn)	22-JUL-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	24-OCT-2008
Amendment	07-NOV-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Perrigo R & D Company
Address:	515 Eastern Avenue Allegan, MI 49010
Representative:	Valerie Gallagher
Telephone:	(269) 673-8451
Facsimile:	(269) 673-7655

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) USAN Name: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg

9. LEGAL BASIS FOR SUBMISSION:

   The RLD is Advil® PM caplets manufactured by Wyeth Consumer Healthcare NDA # 21-394.

There is no unexpired patent for this product.

There is an unexpired exclusivity for this product in the electronic Orange Book.
Exclusivity NC (New Combination) Expiry date 21-DEC-2008.

Perrigo certifies that it will not market the product until the exclusivity expires on 21-DEC-2008.

10. PHARMACOL. CATEGORY: For relief of occasional sleeplessness when associated with minor aches and pains. Aids in falling asleep and staying asleep.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 200 mg/38 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __Rx _X__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed

X Not a SPOTS product

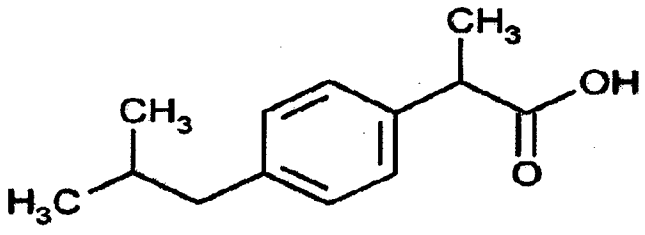
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ibuprofen: $C_{13}H_{18}O_2$: M.W. 206.28

Chemical Name(s): Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-.
(±)-p-Isobutylhydratropic acid.
(±)-2-(p-Isobutylphenyl)propionic acid

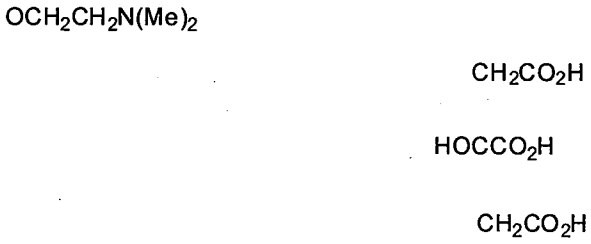
CAS#: 15687-27-1

Molecular Structure:



Diphenhydramine Citrate: $C_{17}H_{21}NO \cdot C_6H_8O_7$ M.W. 491.06
Chemical Name: Ethanamine, 2-(diphenylmethoxy)-N,N-dimethyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).
2-(Diphenylmethoxy)-N,N-dimethylethylamine citrate (1:1)

CAS#: 88637-37-0



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
				1	Adequate.	11-JAN-2008	Reviewed by: Y. Amin
				1	Adequate	12-JAN-2008	Reviewed by: Y. Amin
				4			
				4			
				4			
				4			
			b(4)	4			
				4			
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				4			
				4			

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Advil® PM Ibuprofen/Diphenhydramine Citrate Tablets 200/38 mg	21-394	RLD

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	10-JAN-2008	S. Ferguson.
Methods Validation	N/A		
Labeling	Acceptable	16-JUL-2008	J. Barlow
Bioequivalence	Acceptable	26-JUN-2008	G. Johnson
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 79-113

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC APPROVABLE. Bio, EES and Labeling reviews are acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance Ibuprofen: White or off-white crystalline powder. Freely soluble in ethanol, acetone, chloroform or ethyl ether; insoluble in water Practically insoluble in water. Ibuprofen USP does not exhibit any polymorphism.

Drug Substance Diphenhydramine Citrate: White crystalline powder. Slightly soluble in water and alcohol; insoluble in toluene and acetone.

The drug product: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg are for oral administration.

B. Description of How the Drug Product is Intended to be Used

Oral tablet is for relief of occasional sleeplessness when associated with minor aches and pains. Aids in falling asleep and staying asleep [redacted]. The recommended maximum daily dosage is 2 tablets in 24 hours, (400 mg of Ibuprofen and 76 mg of Diphenhydramine Citrate).

b(4)

C. Basis for Approvability or Not-Approval Recommendation

CMC APPROVABLE. Bio, EES and Labeling reviews are acceptable.

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b(4)

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/s/

Yusuf A. Amin
12/15/2008 09:43:52 AM
CHEMIST

Albert Mueller
12/15/2008 10:30:24 AM
CHEMIST

Dat Doan
12/15/2008 10:31:02 AM
CSO

ANDA 79-113

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

Perrigo R & D Company

Yusuf Amin
OGD – Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 79-113

2. REVIEW #: 2

3. REVIEW DATE: 03-APR-2008

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	17-AUG-2007
Amendment	03-DEC-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	27-MAR-2008
Amendment	11-JUN-2008
Amendment (withdrawn)	22-JUL-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Perrigo R & D Company

Address: 515 Eastern Avenue
Allegan, MI 49010

Representative: Valerie Gallagher

Telephone: (269) 673-8451
Facsimile: (269) 673-7655

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) USAN Name: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Advil® PM caplets manufactured by Wyeth Consumer Healthcare NDA # 21-394.

There is no unexpired patent for this product.

There is an unexpired exclusivity for this product in the electronic Orange Book.
Exclusivity NC (New Combination) Expiry date 21-DEC-2008.

Perrigo certifies that it will not market the product until the exclusivity expires on 21-DEC-2008.

10. PHARMACOL. CATEGORY: For relief of occasional sleeplessness when associated with minor aches and pains. Aids in falling asleep and staying asleep.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 200 mg/38 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __Rx _X__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed

X Not a SPOTS product

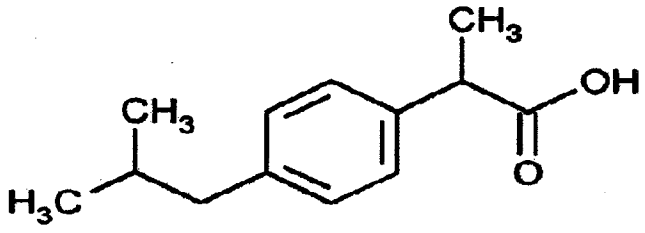
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ibuprofen: $C_{13}H_{18}O_2$: M.W. 206.28

Chemical Name(s): Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-.
(±)-p-Isobutylhydratropic acid.
(±)-2-(p-Isobutylphenyl)propionic acid

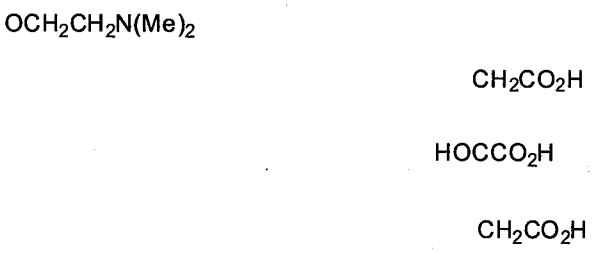
CAS#: 15687-27-1

Molecular Structure:



Diphenhydramine Citrate: $C_{17}H_{21}NO \cdot C_6H_8O_7$ M.W. 491.06
Chemical Name: Ethanamine, 2-(diphenylmethoxy)-N,N-dimethyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).
2-(Diphenylmethoxy)-N,N-dimethylethylamine citrate (1:1)

CAS#: 88637-37-0



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
				1	Adequate.	11-JAN-2008	Reviewed by: Y. Amin
				1	Adequate	12-JAN-2008	Reviewed by: Y. Amin
				4			
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			b(4)	4			
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1 – **DMF Reviewed.**

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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Advil® PM Ibuprofen/Diphenhydramine Citrate Tablets 200/38 mg	21-394	RLD

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Microbiology	N/A		
EES	Acceptable	10-JAN-2008	S. Ferguson.
Methods Validation	N/A		
Labeling	Acceptable	16-JUL-2008	J. Barlow
Bioequivalence	Acceptable	26-JUN-2008	G. Johnson
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 79-113

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC APPROVABLE. EES, Bioequivalence and Labeling reviews are acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance Ibuprofen: White or off-white crystalline powder. Freely soluble in ethanol, acetone, chloroform or ethyl ether; insoluble in water Practically insoluble in water. Ibuprofen USP does not exhibit any polymorphism.

Drug Substance Diphenhydramine Citrate: White crystalline powder. Slightly soluble in water and alcohol; insoluble in toluene and acetone.

The drug product: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg are for oral administration.

B. Description of How the Drug Product is Intended to be Used

Oral tablet is for relief of occasional sleeplessness when associated with minor aches and pains. Aids in falling asleep and staying asleep [redacted] The recommended maximum daily dosage is 2 tablets in 24 hours, (400 mg of Ibuprofen and 76 mg of Diphenhydramine Citrate). b(4)

C. Basis for Approvability or Not-Approval Recommendation

CMC APPROVABLE. EES, Bioequivalence and Labeling reviews are acceptable.

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/s/

Yusuf A. Amin
7/29/2008 06:54:12 AM
CHEMIST
To be TA, [redacted] information required for full approval.

b(4)

Albert Mueller
7/30/2008 08:21:23 AM
CHEMIST

Dat Doan
7/30/2008 12:46:51 PM
CSO

ANDA 79-113

Ibuprofen and Diphenhydramine Citrate Tablets
200 mg/38 mg

Perrigo R & D Company

Yusuf Amin
OGD – Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 79-113

2. REVIEW #: 1

3. REVIEW DATE: 09-JAN-2008

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	17-AUG-2007
Amendment	03-DEC-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Perrigo R & D Company
Address:	515 Eastern Avenue Allegan, MI 49010
Representative:	Valerie Gallagher
Telephone:	(269) 673-8451
Facsimile:	(269) 673-7655

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) USAN Name: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Advil® PM caplets manufactured by Wyeth Consumer Healthcare NDA # 21-394.

There is no unexpired patent for this product.

There is an unexpired exclusivity for this product in the electronic Orange Book.
Exclusivity NC (New Combination) Expiry date 21-DEC-2008.

Perrigo certifies that it will not market the product until the exclusivity expires on 21-DEC-2008.

10. PHARMACOL. CATEGORY: For relief of occasional sleeplessness when associated with minor aches and pains. Aids in falling asleep and staying asleep.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 200 mg/38 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __Rx _X__OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed

X Not a SPOTS product

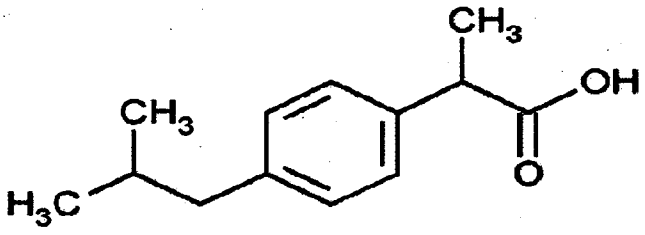
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ibuprofen: $C_{13}H_{18}O_2$: M.W. 206.28

Chemical Name(s): Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-.
(±)-p-Isobutylhydratropic acid.
(±)-2-(p-Isobutylphenyl)propionic acid

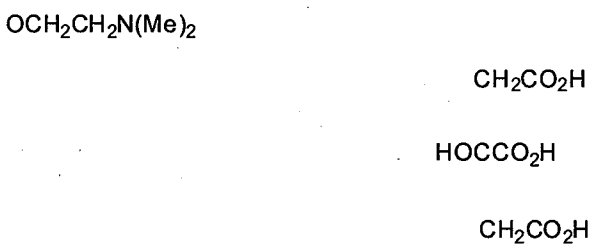
CAS#: 15687-27-1

Molecular Structure:



Diphenhydramine Citrate: $C_{17}H_{21}NO \cdot C_6H_8O_7$ M.W. 491.06
Chemical Name: Ethanamine, 2-(diphenylmethoxy)-N,N-dimethyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).
2-(Diphenylmethoxy)-N,N-dimethylethylamine citrate (1:1)

CAS#: 88637-37-0



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]				1	Adequate.	11-JAN-2008	Reviewed by: Y. Amin
				1	Adequate	12-JAN-2008	Reviewed by: Y. Amin
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				4			
				4			
			b(4)	4			
				4			
				4			
				4			
				4			
				4			
				4			
				4			

[1] Action codes for DMF Table:
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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Advil® PM Ibuprofen/Diphenhydramine Citrate Tablets 200/38 mg	21-394	RLD

18. STATUS:

CONSULTS/ CMC

RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	10-JAN-2008	S. Ferguson.
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 79-113

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is NOT APPROVABLE at this stage. The deficiencies are listed in the letter.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance Ibuprofen: White or off-white crystalline powder. Freely soluble in ethanol, acetone, chloroform or ethyl ether; insoluble in water Practically insoluble in water. Ibuprofen USP does not exhibit any polymorphism.

Drug Substance Diphenhydramine Citrate: White crystalline powder. Slightly soluble in water and alcohol; insoluble in toluene and acetone.

The drug product: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg are for oral administration.

B. Description of How the Drug Product is Intended to be Used

b(4)

Oral tablet is for relief of occasional sleeplessness when associated with minor aches and pains. Aids in falling asleep and staying asleep [redacted] The recommended maximum daily dosage is 2 tablets in 24 hours, (400 mg of Ibuprofen and 76 mg of Diphenhydramine Citrate).

C. Basis for Approvability or Not-Approval Recommendation

The drug product stability specification is not acceptable.

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b(4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yusuf A. Amin
2/27/2008 08:14:13 AM
CHEMIST

Albert Mueller
2/27/2008 12:32:29 PM
CHEMIST

Dat Doan
3/4/2008 11:48:24 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-113

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	79-113	
Drug Product Name	Ibuprofen/ Diphenhydramine Citrate Tablets (OTC)	
Strength(s)	200 mg/ 38 mg	
Applicant Name	Perrigo R & D Company	
Address	515 Eastern Ave Allegan, MI 49010	
Applicant's Point of Contact	Valerie Gallagher	
Contact's Telephone Number	(269) 673 - 8451	
Contact's Fax Number	(269) 673 - 7655	
Original Submission Date(s)	August 17, 2007	
Submission Date(s) of Amendment(s) Under Review	March 27, 2008	
Reviewer	Glendolynn S. Johnson, Pharm.D.	
Study Number (s)	R06-0740	R06-0741
Study Type (s)	Fasting	Non-Fasting
Strength (s)	200 mg/ 38 mg	200 mg/ 38 mg
Clinical Site	PRACS Institute , Ltd.	
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104	
Analytical Site	PRACS Institute , Ltd.	
Analytical Site Address	4801 Amber Valley Parkway Fargo, ND 58104	
OUTCOME DECISION	**ACCEPTABLE**	

1 EXECUTIVE SUMMARY

This application contains the results of the fasting and fed bioequivalence (BE) studies comparing the test product, Ibuprofen/ Diphenhydramine Citrate Tablets, 200 mg/ 38 mg, to the corresponding reference product, Advil PM® (ibuprofen/diphenhydramine citrate) Caplets, 200 mg/ 38 mg (OTC). It should be noted that the DBE recommends only the fasted study for this drug product. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects. The firm's fasting and fed studies are acceptable. The results are summarized in the tables below.

A. Ibuprofen

Ibuprofen/Diphenhydramine Tablets 1 x 200 mg/ 38 mg tablet Fasting Bioequivalence Study No. (R06-0740), N= 44 (Male=19 and Female=25) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr-ng/ml)	75110.36	77094.39	0.97	95.43	99.47
AUC∞ (hr-ng/ml)	75948.44	77950.40	0.97	95.41	99.50
Cmax (ng/ml)	20400.03	22385.61	0.91	86.38	96.14

Ibuprofen/Diphenhydramine Tablets 1 x 200 mg/ 38 mg tablet Fed Bioequivalence Study No. (R06-0741), N=44 (Male=15 and Female=29) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr-ng/ml)	61181.42	63721.44	0.96	93.49	98.60
AUC∞ (hr-ng/ml)	61958.52	64540.36	0.96	93.47	98.60
Cmax (ng/ml)	15446.87	16451.19	0.94	87.60	100.64

B. Diphenhydramine

Ibuprofen/Diphenhydramine Tablets 1 x 200 mg/ 38 mg tablet Fasting Bioequivalence Study No. (R06-0740), N= 44 (Male=19 and Female=25) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr-ng/ml)	318.03	318.21	1.00	96.81	103.18
AUC∞ (hr-ng/ml)	337.11	335.17	1.01	97.54	103.71
Cmax (ng/ml)	37.97	38.05	1.00	95.54	104.23

Ibuprofen/Diphenhydramine Tablets 1 x 200 mg/ 38 mg tablet Fed Bioequivalence Study No. (R06-0741), N=43 (Male=14 and Female=29) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr-ng/ml)	318.10	351.02	0.91	85.36	96.20
AUC∞ (hr-ng/ml)	333.99	363.64	0.92	86.31	97.74
Cmax (ng/ml)	37.57	42.55	0.88	83.99	92.83

The dissolution testing was reviewed previously. The firm has conducted acceptable comparative dissolution testing using the DBE-recommended dissolution method (DFS N 079113 N 000 AB 13-Feb-2008). On March 27, 2008, the firm had acknowledged its acceptance of the DBE-recommended dissolution testing method and specification of NLT (b) (4) (Q) in 30 minutes for both Ibuprofen and Diphenhydramine.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is **acceptable.**

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg (OTC)
Reference Product	Advil PM® Caplets, 200 mg/38 mg. (OTC)
RLD Manufacturer	Wyeth Consumer Healthcare
NDA No.	21-394
RLD Approval Date	Approved December 21, 2005
Indication	Indicated to help with sleeplessness due to minor aches and pains. Diphenhydramine is an antihistamine that causes drowsiness and ibuprofen reduces inflammation and helps relieve minor aches and pains1 in adults and children ≥ 12 years old.

3.2 PK/PD Information

Bioavailability	Oral, immediate-release ibuprofen bioavailability (BA) is, at highest, 92% which indicates that it is well absorbed. The BA of the active form S (+) ibuprofen is highest following administration of the pure S (+) enantiomer. Racemic ibuprofen produces S (+) bioavailability of 71% and R (-) ibuprofen produces S (+) BA of 58%. Considerable R (-) ibuprofen is converted to S (+) ibuprofen *in vivo*[2]. Ibuprofen is approximately 80% absorbed from the gut[3]. Oral BA of diphenhydramine ranges from 65 – 100%2. Diphenhydramine is highly protein-bound[3]. With single doses up to 800 mg, a linear relationship exists between the amount of ibuprofen administered and the area under the curve. Above 800 mg, however, the area under the curve increases less than proportional to increases in dose. There is no evidence of drug accumulation or enzyme induction.[4]
Food Effect	Although the peak concentration is lower and time to peak concentration is slower if the drug is taken with food, the extent of ibuprofen absorption is not affected[3]. No food effect for diphenhydramine or ibuprofen is listed in the labeling.
Tmax	Peak concentrations of ibuprofen are reached at roughly 120 minutes following tablet administration[3]. Peak concentrations of diphenhydramine are reached within 2-4 hours[3].
Metabolism	Ibuprofen does undergo hepatic metabolism through oxidation by cytochrome P450 2C9 to two inactive metabolites[3].

[1] www.drugdigest.org
[2] www.csi micromedex.com
[3] http://www.clinicalpharmacology-ip.com – Diphenhydramine; Ibuprofen
[4] www.rxlist.com/cgi/generic/ibup_cp.htm

	Diphenhydramine metabolism occurs in the liver to produce mainly diphenylmethoxyacetic acid, which then becomes conjugated; other metabolites are also formed. Diphenhydramine's metabolites include diphenylmethane (inactive), N,N-dimethyl-diphenhydramine (inactive), N,N-di-demethyl-diphenhydramine (inactive), diphenylmethoxy acetic acid (inactive), monodesmethyldiphenhydramine (inactive). Approximately 50% of diphenhydramine is metabolized in the liver to diphenylmethane, which suggests a large first-pass effect[3].
Excretion	Ibuprofen is excreted in the urine, 50 – 60% as metabolites and approximately 10% as unchanged drug. Some biliary excretion may occur[3]. Approximately 37% of the dose is excreted in 24 hours as metabolite 2-(p-(2carboxy-propyl)phenyl) propionic acid and 25% as metabolite2-(p-(2hydroxymethyl-propyl)phenyl) propionic acid[2]. Little, if any, diphenhydramine is excreted unchanged in urine. Metabolites of diphenhydramine are reported to be eliminated less rapidly than unchanged drug with 50 to 65% if these compounds recovered in the urine as diphenylmethane derivatives. Urinary excretion of total diphenhydramine metabolites represented 64% of a dose in single dose studies and 49% after multiple doses[3]. Most unchanged drug and metabolites are excreted within 24 hours of oral administration[3].
Half-life	Ibuprofen plasma half-life is between 2-8 hours. Diphenhydramine plasma half-life is between 2-4 hours.
Drug Specific Issues (if any)	None

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	1, fasting

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	200 mg/ 38 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	None

Analytes to measure (in plasma/serum/blood):	Ibuprofen and Diphenhydramine in plasma
Bioequivalence based on:	(90% CI) Parent compound, Ibuprofen and Diphenhydramine
Waiver request of in-vivo testing:	none
Source of most recent recommendations:	Control # 06-0321 Perrigo
Summary of OGD or DBE History (for details, see Appendix 4.4):	Control Documents received: C060321 (Perrigo-03/06/06) The current Orange Book includes no approved ANDAs for Ibuprofen/Diphenhydramine 200mg/38 mg Tablets (OTC).

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	- -	- -
In vitro dissolution	Yes	1
Waiver requests	No	- -
BCS Waivers	- -	- -
Clinical Endpoints	- -	- -
Failed Studies	- -	- -
Amendments	Yes	1 (dissolution acknowledgement)

Note[5]: Because no food effect is mentioned in the RLD labeling, only a fasting study is recommended for the drug product (see control 06-0321). Perrigo submitted this ANDA with both fasted and fed studies on August 17, 2007, while DBE's review (recommending only fasted study for this drug product) was completed on September 21, 2007.

[5] Control 060321c0306

3.5 Pre-Study Bioanalytical Method Validation

A. Ibuprofen

Information Requested	Data
Analyte	Ibuprofen
Internal standard (IS)	(b) (4)
Method description	Solid Phase Extraction
Limit of quantitation	100.00 ng/mL
Average recovery of drug (%)	74.46%
Average recovery of IS (%)	72.85%
Standard curve concentrations (ng/mL)	100.00, 500.00, 1000.00, 5000.00, 10000.00, 20000.00, 30000.00, 40000.00 ng/mL
QC concentrations (ng/mL)	300.00, 15000.00, 35000.00 ng/mL
QC Intraday precision range (%)	0.73% – 2.06%
QC Intraday accuracy range (%)	92.68% – 105.26%
QC Interday precision range (%)	1.67% – 3.59%
QC Interday accuracy range (%)	102.21% – 108.74%
Bench-top stability (hrs:mins)	25:29 hours :minutes @ room temperature
Stock stability (hrs:mins)	168:18 hours:minutes @ 4°C, 19:49 hours:minutes at room temperature
Processed stability (hrs:mins)	96:00 hours :minutes @ 4°C
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	63 days @ -20°C
Dilution integrity	50000.00 ng/mL diluted 3:1 / 1:10 99.00% / 97.00%
Selectivity	No interfering peaks noted in six blank plasma samples

B. Diphenhydramine

Information Requested	Data
Analyte	Diphenhydramine
Internal standard (IS)	(b) (4)
Method description	Liquid/liquid extraction
Limit of quantitation	0.50 ng/mL
Average recovery of drug (%)	94.0%
Average recovery of IS (%)	71.9%
Standard curve concentrations (ng/mL)	0.50, 1.00, 5.00, 10.00, 50.00, 100.00, 150.00, 175.00, 200.00 ng/mL
QC concentrations (ng/mL)	1.50, 80.00, 160.00, 20.00 ng/mL
QC Intraday precision range (%)	1.19% – 4.72%
QC Intraday accuracy range (%)	90.3% – 100.2%
QC Interday precision range (%)	3.04% – 4.53%
QC Interday accuracy range (%)	93.7% – 95.9%
Bench-top stability (hrs:mins)	19:06 hours :minutes @ room temperature
Stock stability (hrs:mins)	95:27 hours:minutes @ 4°C and room temperature
Processed stability (hrs:mins)	43:22 hours :minutes @ 4°C
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	113 days @ -20°C
Dilution integrity	200.00 ng/mL 3:1 / 1:1 / 1:3 100.0% / 101.0% / 102.0%
Selectivity	No interfering peaks noted in ten blank plasma samples

Note: The Diphenhydramine QC concentration of 20.00 ng/mL represents the Blind QC.

SOPs submitted	Yes
Bioanalytical method is acceptable	Acceptable

Comments on the Pre-Study Method Validation:

1. The frozen, long-term stability data of 63 days for ibuprofen and 113 days for diphenhydramine exceed the storage period for both the fasted (38 days for ibuprofen and 50 days for diphenhydramine) and fed (47 days for ibuprofen and 51 days for diphenhydramine) BE studies.

2. Quality Control samples were prepared with drug free human plasma using EDTA as anticoagulant.

3. Dilution Integrity: Ibuprofen (50000.00 ng/ mL) 3:1 dilutions: % nominal 99.0 and % CV 1.00 and Ibuprofen 1:10 dilutions: % nominal 97.00 and % CV 2.00. Diphenhydramine (200 ng/ mL) 3:1 dilutions: % nominal 100 and % CV 3.00, Diphenhydramine 1:1 dilutions: % nominal 101 and % CV 2.00 and Diphenhydramine 1:3 dilutions: % nominal 102 and % CV 4.00.

4. The pre-study method validation is acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

A. Ibuprofen

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects[1] No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters[1] Median (Range) for T_{max}					
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng-hr/mL)	AUC_{0-8} (ng-hr/mL)	$t_{1/2}$ (hr)	k_e (1/hr)
R06-0740	A Relative Bioavailability Study of 200 mg/38 mg Ibuprofen/ Diphenhydramine Citrate Tablets vs. Caplets under Fasting Conditions	Open, randomized, two-way crossover, single 200 mg/38 mg dose	Test: Ibuprofen/Diphenhydramine Citrate 200 mg/38 mg Tablets, Oral [Batch No. 7D1728]	44 (19/25) Healthy Volunteers 33.48 yr (18 - 77 yr)	20800.68 (19.85)	1.5 (0.67-4.5)	77192.71 (23.81)	78068.86 (24.01)	2.29 (11.25)	0.3067 (11.22)
			Reference: ADVIL® PM 200 mg/38 mg Caplets, Oral [Lot No. B59856]		22865.68 (20.63)	1.5 (0.33-4.5)	79131.77 (23.16)	80013.51 (23.23)	2.31 (11.39)	0.3037 (12.14)
R06-0741	A Relative Bioavailability Study of 200 mg/38 mg Ibuprofen/ Diphenhydramine Citrate Tablets vs. Caplets under Non-Fasting Conditions	Open, randomized, two-way crossover, single 200 mg/38 mg dose	Test: Ibuprofen/Diphenhydramine Citrate 200 mg/38 mg Tablets, Oral [Batch No. 7D1728]	44 (15/29) Healthy Volunteers 28.41 yr (18 - 75 yr)	15901.45 (24.36)	1.5 (0.67-4.5)	62311.82 (19.38)	63106.1 (19.5)	2.18 (12.79)	0.3228 (13.87)
			Reference: ADVIL® PM 200 mg/38 mg Caplets, Oral [Lot No. B59856]		17065.59 (28.25)	1.75 (0.67-4)	65031.28 (20.07)	65870.15 (20.1)	2.22 (12.71)	0.3177 (14.02)

[1]Subjects used in final statistical report

B. Diphenhydramine

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects[1] No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters[1] Median (Range) for T_{max}					
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng-hr/mL)	AUC_{0-8} (ng-hr/mL)	$t_{1/2}$ (hr)	k_e (1/hr)
R06-0740	A Relative Bioavailability Study of 200 mg/38 mg Ibuprofen/ Diphenhydramine Citrate Tablets vs. Caplets under Fasting Conditions	Open, randomized, two-way crossover, single 200 mg/38 mg dose	Test: Ibuprofen/Diphenhydramine Citrate 200 mg/38 mg Tablets, Oral [Batch No. 7D1728] Reference: ADVIL® PM 200 mg/38 mg Caplets, Oral [Lot No. B59856]	44 (19/25) Healthy Volunteers 33.48 yr (18 - 77 yr)	40.35 (35.68)	2.25 (1.25 - 5)	349.14 (44.68)	370.93 (45.76)	10.46 (24.92)	0.0706 (26.57)
					40.53 (36.73)	2.5 (1.25 - 4.5)	350.37 (45.8)	371.08 (47.41)	10.54 (27.54)	0.0713 (31.68)
R06-0741	A Relative Bioavailability Study of 200 mg/38 mg Ibuprofen/ Diphenhydramine Citrate Tablets vs. Caplets under Non-Fasting Conditions	Open, randomized, two-way crossover, single 200 mg/38 mg dose	Test: Ibuprofen/Diphenhydramine Citrate 200 mg/38 mg Tablets, Oral [Batch No. 7D1728] Reference: ADVIL® PM 200 mg/38 mg Caplets, Oral [Lot No. B59856]	43 (14/29) Healthy Volunteers 28.00 yr (18 - 75 yr)	40.91 (35.47)	2.5 (1.5 - 4.5)	357.22 (49.86)	382.17 (53.91)	10.34 (29.65)	0.0783 (70.36)
					46.41 (40.16)	2.5 (1.25 - 48)	401.45 (58.76)	384.26 (38.93)	9.73 (24.71)	0.0831 (82.76)

[1]Subjects used in final statistical report

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

A. Ibuprofen

Ibuprofen/Diphenhydramine Tablets 1 x 200 mg/ 38 mg tablet Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Fasting Bioequivalence Study No. R06-0740					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr-ng/ml)	75110.36	77094.39	0.97	95.43	99.47
AUC∞ (hr-ng/ml)	75948.44	77950.40	0.97	95.41	99.50
Cmax (ng/ml)	20400.03	22385.61	0.91	86.38	96.14

Ibuprofen/Diphenhydramine Tablets 1 x 200 mg/ 38 mg tablet Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Fed Bioequivalence Study No. R06-0741					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr-ng/ml)	61181.42	63721.44	0.96	93.49	98.60
AUC∞ (hr-ng/ml)	61958.52	64540.36	0.96	93.47	98.60
Cmax (ng/ml)	15446.87	16451.19	0.94	87.60	100.64

B. Diphenhydramine

Ibuprofen/Diphenhydramine Tablets 1 x 200 mg/ 38 mg tablet Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Fasting Bioequivalence Study No. R06-0740					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr-ng/ml)	318.03	318.21	1.00	96.81	103.18
AUC∞ (hr-ng/ml)	337.11	335.17	1.01	97.54	103.71
Cmax (ng/ml)	37.97	38.05	1.00	95.54	104.23

Ibuprofen/Diphenhydramine Tablets 1 x 200 mg/ 38 mg tablet Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Fed Bioequivalence Study No. R06-0741					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr-ng/ml)	318.10	351.02	0.91	85.36	96.20
AUC∞ (hr-ng/ml)	333.99	363.64	0.92	86.31	97.74
Cmax (ng/ml)	37.57	42.55	0.88	83.99	92.83

Table 3. Reanalysis of Study Samples

A. Ibuprofen

Reason for Reanalysis	R06-0740 Additional Information in Volume(s), Page(s)							
	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis[5]			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=836[2]	Reference N=836[2]	Test N=836[2]	Reference N=836[2]	Test N=836[2]	Reference N=836[2]	Test N=836[2]	Reference N=836[2]
	n[3]	n[3]	%[4]	%[4]	n[3]	n[3]	%[4]	%[4]
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Peak In Pre-Dose	5	7	0.6	0.8	5	7	0.6	0.8
High Internal Standard	1	0.0	0.1	0.0	1	-	0.1	-
Total Number of Samples Reanalyzed	6	7	0.7	0.8	6	7	0.7	0.8

Reason for Reanalysis	R06-0741 Additional Information in Volume(s), Page(s)							
	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis[5]			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=835	Reference N=835	Test N=835	Reference N=835	Test N=835	Reference N=835	Test N=835	Reference N=835
	n[3]	n[3]	%[4]	%[4]	n[3]	n[3]	%[4]	%[4]
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
High Internal Standard	1	1	0.1	0.1	1	-	0.1	-
Poor Chromatography	1	2	0.1	0.2	1	2	0.1	0.2
Low Internal Standard	0.0	2	0.0	0.2	-	1	-	0.1
Total Number of Samples Reanalyzed	2	5	0.2	0.6	2	3	0.2	0.4

B. Diphenhydramine

Reason for Reanalysis	R06-0740 Additional Information in Volume(s), Page(s)							
	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis[5]			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=966[2]	Reference N=968[2]	Test N=966[2]	Reference N=968[2]	Test N=966[2]	Reference N=968[2]	Test N=966[2]	Reference N=968[2]
	n[3]	n[3]	%[4]	%[4]	n[3]	n[3]	%[4]	%[4]
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Low Internal Standard Response	27	33	2.8	3.4	22	25	2.3	2.6
High Internal Standard Response	38	47	3.9	4.9	32	38	3.3	3.9
High Internal Standard Response, High Internal Standard Response	4	5	0.4	0.5	4	5	0.4	0.5
Total Number of Samples Reanalyzed	69	85	7.1	8.8	58	68	6.0	7.0

Reason for Reanalysis	R06-0741 Additional Information in Volume(s), Page(s)							
	Number of Samples Reanalyzed				Number of Recalculated Values Used After Reanalysis[5]			
	Actual Number		% of Total Assays		Actual Number		% of Total Assays	
	Test N=965[2]	Reference N=966[2]	Test N=965[2]	Reference N=966[2]	Test N=965[2]	Reference N=966[2]	Test N=965[2]	Reference N=966[2]
	n[3]	n[3]	%[4]	%[4]	n[3]	n[3]	%[4]	%[4]
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Adjusted LLOQ	10	11	1.0	1.1	1	3	0.1	0.3
Low Internal Standard Response (LIS)	6	22	0.6	2.3	3	20	0.3	2.1
High Internal Standard Response (HIS)	21	21	2.2	2.2	15	16	1.6	1.6
LIS, Peak in Pre-Dose, LIS (x3)	0.0	1	0.0	0.1	-	1	-	0.1
Repeat by Error	56	46	5.8	4.8	-	-	-	-
Peak in Pre-Dose, repeated by error in singlet instead of triplicate	2	0.0	0.2	0.0	2	-	0.2	-
HIS, HIS	2	1	0.2	0.1	2	-	0.2	-
Peak in Pre-Dose	0.0	3	0.0	0.3	-	3	-	0.3
HIS (Peak In Pre-Dose)	1	0.0	0.1	0.0	1	-	0.1	-
HIS (Repeated by error in triplicate instead of singlet)	1	0.0	0.1	0.0	-	-	-	-
Total Number of Samples Re analyzed	99	105	10.3	10.9	24	43	2.5	4.5

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout the table
[2] N = Number of samples analyzed for each treatment
[3] n = Number of samples repeated
[4] % = percentage of assays repeated (i.e. 100*(n/N)%)
[5] Reported values that are different from the original value

Did use of recalculated plasma concentration data change study outcome? No PK repeats

Comments from the Reviewer: Acceptable

1. For the fasting study (R06-0740), the firm has provided the following reason for the reported concentrations: only valid results. This reason illustrates why the "Number of Samples Reanalyzed" differ from the Number of Recalculated Values Used After Reanalysis". In addition, for the reassay samples with the reasons of "Low Internal Standard Response" and "High Internal Standard Response", the reviewer has compared the original assay and reported reassay results and found

that < 2% (2 samples) of the recalculated values differed > 20% from the original values. The reviewer reanalyzed the data using the original values of these 2 samples and the 90% confidence intervals still remained within the acceptable range.

2. For the fed study (R06-0741), the firm has provided the following reasons for reported concentrations: only valid result, median of all acceptable results, original value and median of all results. These reasons illustrate why the "Number of Samples Reanalyzed" differ from the Number of Recalculated Values Used After Reanalysis". In addition, for the reassay samples with the reasons of "Low Internal Standard Response" and "High Internal Standard Response", the reviewer has compared the original assay and reported reassay results and found that < 6% (3 samples) of the recalculated values differed > 20% from the original values. The reviewer reanalyzed the data of these 3 samples using the original values and the 90% confidence intervals still remained within the acceptable range.

3.7 Formulation

Location in appendix	Section 4.2, Page 50
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	**ACCEPTABLE**
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DFS: N 079113 N 000 AB 13-Feb-2008
Source of Method (USP, FDA or Firm)	FDA-recommended method
Medium	50 mM Phosphate buffer, pH 6.5
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
DBE-recommended specifications	NLT (b) (4) (Q) in 30 minutes for ibuprofen and diphendydramine
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	N/A
If no, reason why F2 not calculated	Rapidly dissolving
Is method acceptable?	METHOD ACCEPTABLE
If not then why?	N/A

3.9 Waiver Request(s)

None

3.10 Deficiency Comments

None

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (R06-0740) acceptable. Perrigo R & D Company, conducted the fasting BE study on its test product, Ibuprofen / Diphenhydramine Tablet, 200 mg/ 38 mg , (lot # 7D1728) comparing it to Wyeth's Advil PM® Caplet, 200 mg/ 38 mg (lot # B59856).

2. The Division of Bioequivalence finds the non-fasting BE study (R06-0741) acceptable. Perrigo R & D Company conducted the non-fasting BE study on its test product, Ibuprofen/ Diphenhydramine Tablet, 200 mg/ 38 mg, (lot # 7D1728) comparing it to Wyeth's Advil PM® Caplet, 200 mg/ 38 mg (lot # B59856).

3. The firm's *in vitro* dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of 50 mM Phosphate buffer, pH 6.5 at 37ºC ± 0.5ºC using USP apparatus 2 (paddle) at 50 rpm. The test product should meet the following specification(s): NLT (b) (4) % (Q) of both drug components in the dosage form is dissolved in 30 minutes.

4. This application is **acceptable**.

3.12 Comments for O (b) (6) iplines

Discipline	Comment
None	- -

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

A. Ibuprofen

Study Number	R06-0740
Study Title	A Relative Bioavailability Study of 200 mg/38 mg Ibuprofen/Diphenhydramine Citrate Tablets vs. Caplets Under Fasting Conditions
Clinical Site (Name, Address, Phone #)	PRACS Institute, Ltd. 4801 Amber Valley Parkway Fargo, ND 58104 (701) 239-4750
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I: 13 May 2007
	Period II: 20 May 2007
Analytical Site (Name, Address, Phone #)	PRACS Institute, Ltd. 4801 Amber Valley Parkway Fargo, ND 58104 (701) 239-4750
Analysis Dates	June 12, 2007 – June 20, 2007
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	38 days

B. Diphenhydramine

Study Number	R06-0740
Study Title	A Relative Bioavailability Study of 200 mg/38 mg Ibuprofen/Diphenhydramine Citrate Tablets vs. Caplets Under Fasting Conditions
Clinical Site (Name, Address, Phone #)	PRACS Institute, Ltd. 4801 Amber Valley Parkway Fargo, ND 58104 (701) 239-4750
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I: 13 May 2007
	Period II: 20 May 2007
Analytical Site (Name, Address, Phone #)	PRACS Institute, Ltd. 4801 Amber Valley Parkway Fargo, ND 58104 (701) 239-4750
Analysis Dates	June 14, 2007 – July 2, 2007
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	50 days

Table 5. Product information

Product	**Test**		**Reference**	
Treatment ID	R06-0740 & R06-0741		R06-0740 & R06-0741	
Product Name	Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/ 38 mg		Advil® PM Caplets	
Manufacturer	Perrigo R&D Company		Wyeth Consumers Healthcare	
Batch/Lot No.	7D1728		B59856	
Manufacture Date	04/16/2007		N/A	
Expiration Date	N/A		04/09	
Strength	Ibuprofen: 200 mg Diphenhydramine Citrate: 38 mg		Ibuprofen: 200 mg Diphenhydramine Citrate: 38 mg	
Dosage Form	Tablet (caplet)		Tablet (caplet)	
Bio-batch Size	(b) (4)		N/A	
Production Batch Size	(b) (4)		N/A	
Potency	Ibuprofen: (b) (4) Diphenhydramine Citrate: (b) (4)		Ibuprofen: (b) (4) Diphenhydramine Citrate: (b) (4)	
Content Uniformity (mean, %CV)	Ibuprofen	Mean: 99.7% RSD: 1.5% AV: 3.6	Ibuprofen	Mean: 102.6% RSD: 1.8% AV: 5.4
	Diphenhydramine Citrate	Mean: 97.2% RSD: 1.5% AV: 4.9	Diphenhydramine Citrate	Mean: 99.2% RSD: 4.5% AV: 10.8
Dose Administered	One tablet per subject per dosing period		One tablet per subject per dosing period	
Route of Administration	Oral		Oral	

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

No. of Subjects	44 subjects enrolled and completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1 group
Washout Period	At least 7 days
Randomization Scheme	AB: 1, 2, 3, 5, 6, 14, 15, 20, 22, 24, 25, 26, 27, 29, 31, 32, 33, 34, 35, 36, 38, 41 and 44 BA: 4, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 19, 21, 23, 25, 28, 30, 37, 39, 40, 42 and 43
Blood Sampling Times	Pre-dose (0), 0.167, 0.33, 0.67, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00*, 36.00* and 48.00* hours post-dose
Blood Volume Collected/Sample	One (b) (4) was used to collect for ibuprofen and diphenhydramine. 22 blood samples per period x 2 study periods (total of 44 samples, 440 mL total volume).
Blood Sample Processing/Storage	The blood samples were collected in (b) (4) The plasma samples for study hour 0.167 through 16 were (b) (4) (one for ibuprofen and one for diphenhydramine). The plasma samples for study hour 24 though 48 were (b) (4) (diphenhydramine only). The plasma samples were (b) (4) or colder until shipment for sample analysis.
IRB Approval	Yes, March 28, 2007
Informed Consent	Yes, March 28, 2007
Length of Fasting	An overnight fast of at least 10.5 hours prior to dose administration after which a fast (except water) was maintained until at least 4 hours after dosing.
Length of Confinement	For at least 10.5 hours prior to drug administration until 24 hours post dose. Volunteers returned to the clinical site for the 36 hour and 48 hour blood sample.
Safety Monitoring	The subjects were monitored throughout the confinement portion of the study. Blood pressure and heart rate were measured prior to dosing and at 24 hours after each dose.

* For diphenhydramine only

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

R06-0740			
		Treatment Groups	
		Test Product N=44[1]	Reference Product N=44[1]
Age (years)	Mean ± SD	33.48 ± 15.81	33.48 ± 15.81
	Range	18 - 77	18 - 77
Age Groups	< 18	-	-
	18 – 39	30 (68.18%)	30 (68.18%)
	40 – 64	12 (27.27%)	12 (27.27%)
	65 – 75	1 (2.27%)	1 (2.27%)
	> 75	1 (2.27%)	1 (2.27%)
Sex	Male	19 (43.18%)	19 (43.18%)
	Female	25 (56.82%)	25 (56.82%)
Hispanic or Latino Race	N	-	-
	A	-	-
	B	-	-
	I	-	-
	W	2 (4.55%)	2 (4.55%)
		1 (2.27%)	1 (2.27%)
Not Hispanic or Latino Race	N	1 (2.27%)	1 (2.27%)
	A	1 (2.27%)	1 (2.27%)
	B	-	-
	I	-	-
	W	39 (88.64%)	39 (88.64%)
BMI	Mean ± SD	25.61 ± 3.59	25.61 ± 3.59
	Range	19.4 - 31.9	19.4 - 31.9
Other Factors			

[1]Subjects used in final statistical report

RACE:

American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W

Table 8. Dropout Information, Fasting Bioequivalence Study

R06-0740				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
None	N/A	N/A	N/A	N/A

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event[1]	**Reported Incidence by Treatment Groups R06-0740**	
	Test N=44[2] **n (%)**[3]	**Reference N=44**[2] **n (%)**[3]
Nervous system disorders		
Headache	-	1 (2.27%)
Respiratory, thoracic and mediastinal disorders		
Nasopharyngitis	1 (2.27%)	-
Total Subjects Reporting at Least One Adverse Event	1 (2.27%)	1 (2.27%)

[1] MedDRA Version 9.1
[2] N = Number of subjects dosed for each treatment
[3] n = Number of subjects reporting at least one incidence of respective adverse event;
(%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

R06-0740		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Concomitant medications	N/A	24

Comments on Dropouts/Adverse Events/Protocol Deviations:

1. No serious adverse events (SAEs) were reported during the fasting BE study.

2. According to the firm, one (1) subject experienced an adverse event that required the use of concomitant medications during the course of this study. Subjects # 24 experienced the event headache and took ibuprofen once on 5/15/07.

3. Several blood sampling deviations were recorded. The blood sampling time deviations were insignificant.

4. No subject experienced emesis during the fasting study.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

A. Ibuprofen

R06-0740 Ibuprofen									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	100.0	200.0	500.0	1000	5000	10000	20000	30000	40000
Interday Precision (%CV)	1.8	1.6	2.1	2.9	2.3	2.6	4.3	3.1	2.7
Interday Accuracy (%Deviation)	1.0	-1.3	-0.5	-2.4	1.1	-1.1	1.8	2.0	-0.6
Linearity	0.9977 – 0.9995								
Linearity Range (ng/mL)	100.0 – 40000								
Sensitivity/LOQ (ng/mL)	100.0								

R06-0740 Ibuprofen				
Parameter	**Quality Control Samples**			
Concentration (ng/mL)	300.0	3000	18000	28000
Interday Precision (%CV)	3.1	2.1	2.4	3.0
Interday Accuracy (%Deviation)	-3.1	-2.9	-1.8	-1.5

Reviewer's Note: Two samples of the inter-run CV for the low QCs exceeds the [redacted]% acceptance criteria. The statistics for the low QCs were re-calculated excluding all of the failed low QCs and can be seen in the table above.

(b) (4)

B. Diphenhydramine

R06-0740
Diphenhydramine

Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	0.5000	1.000	5.000	10.00	50.00	100.0	150.0	175.0	200.0
Interday Precision (%CV)	7.5	4.8	4.1	3.7	3.7	3.2	3.6	2.9	3.3
Interday Accuracy (%Deviation)	-5.6	2.4	0.9	2.8	-0.2	-0.4	-0.3	0.5	-0.1
Linearity	0.9975 – 0.9995								
Linearity Range (ng/mL)	0.5000 – 200.0								
Sensitivity/LOQ (ng/mL)	0.5000								

R06-0740
Diphenhydramine

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	1.500	20.00	80.00	160.0
Interday Precision (%CV)	8.4	4.5	4.3	3.9
Interday Accuracy (%Deviation)	8.5	9.0	11.0	4.5

Comments on Study Assay Validation:

Acceptable

Any interfering peaks in chromatograms? No

Were 20% of chromatograms included? Yes

Were chromatograms serially or randomly selected? Serially

Comments on Chromatograms:

Acceptable

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
406_05 Version 01	February 19, 2007	Sample Reanalysis and Reporting Criteria

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed? Yes

Did recalculation of PK parameters change the study outcome? No

Does the reviewer agree with the outcome of the repeat assays?	Agree
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

Acceptable

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

A. Ibuprofen

Fasting Bioequivalence Study No . R06-0740									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr*ng/ml)	77192.71	23.81	42570.41	127403.3	79131.77	23.16	44277.13	125562.6	0.98
AUC∞ (hr*ng/ml)	78068.86	24.01	43633.45	130930.4	80013.51	23.23	44674.73	128154.9	0.98
Cmax (ng/ml)	20800.68	19.85	13100.00	31610.00	22865.68	20.63	12720.00	35900.00	0.91
Tmax* (hr)	1.50	.	0.67	4.50	1.50	.	0.33	4.50	1.00
Kel (hr^{-1})	0.31	11.22	0.24	0.39	0.30	12.14	0.24	0.42	1.01
T1/2 (hr)	2.29	11.25	1.76	2.92	2.31	11.39	1.64	2.87	0.99

* Tmax values are presented as median, range

B. Diphenhydramine

Fasting Bioequivalence Study No. R06-0740									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	349.14	44.68	126.72	782.15	350.37	45.80	130.35	811.99	1.00
AUC∞ (hr *ng/ml)	370.93	45.76	138.10	862.63	371.08	47.41	135.81	898.64	1.00
Cmax (ng/ml)	40.35	35.68	17.05	84.77	40.53	36.73	18.73	89.05	1.00
Tmax* (hr)	2.25	.	1.25	5.00	2.50	.	1.25	4.50	0.90
Kel (hr^{-1})	0.07	26.57	0.04	0.13	0.07	31.68	0.04	0.16	0.99
T1/2 (hr)	10.46	24.92	5.22	15.59	10.54	27.54	4.22	16.57	0.99

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

A. Ibuprofen

IBUPROFEN/DIPHENHYDRAMINE CITRATE TABLETS 200 mg/38 mg (1 x 200 mg/38 mg) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Fasting Bioequivalence Study (R06-0740) N=44[2]				
Parameter	Test	Reference	% Ratio	90% C.I.
AUC_{0-t}	75110.36	77094.39	97.43	(95.43, 99.47)
$AUC_{0-\infty}$	75948.44	77950.40	97.43	(95.41, 99.5)
C_{max}	20400.03	22385.61	91.13	(86.38, 96.14)

B. Diphenhydramine

IBUPROFEN/DIPHENHYDRAMINE CITRATE TABLETS 200 mg/38 mg (1 x 200 mg/38 mg) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Fasting Bioequivalence Study (R06-0740) N=44[2]				
Parameter	Test	Reference	% Ratio	90% C.I.
AUC_{0-t}	318.03	318.21	99.94	(96.81, 103.18)
$AUC_{0-\infty}$	337.11	335.17	100.58	(97.54, 103.71)
C_{max}	37.97	38.05	99.79	(95.54, 104.23)

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

A. Ibuprofen

Ibuprofen/Diphenhydramine Tablets
1 x 200 mg/ 38 mg tablet
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals
Fasting Bioequivalence Study No. R06-740

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	75110.36	77094.39	0.97	95.43	99.47
AUC∞ (hr *ng/ml)	75948.44	77950.40	0.97	95.41	99.50
Cmax (ng/ml)	20400.03	22385.61	0.91	86.38	96.14

B. Diphenhydramine

Ibuprofen/Diphenhydramine Tablets
1 x 200 mg/ 38 mg tablet
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals
Fasting Bioequivalence Study No. R06-740

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	318.03	318.21	1.00	96.81	103.18
AUC∞ (hr *ng/ml)	337.11	335.17	1.01	97.54	103.71
Cmax (ng/ml)	37.97	38.05	1.00	95.54	104.23

Table 17. Additional Study Information, Fasting Study No. R06-0740

Root mean square error, AUC0-t	0.0579 Ibuprofen 0.0889 Diphenhydramine	
Root mean square error, AUC∞	0.0585 Ibuprofen 0.0855 Diphenhydramine	
Root mean square error, Cmax	0.1492 Ibuprofen 0.1215 Diphenhydramine	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	44	44
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	4 (Ibuprofen) 0 (Diphenhydramine)	5 (Ibuprofen) 0 (Diphenhydramine)
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞					
Treatment		**n**	**Mean**	**Minimum**	**Maximum**
Test	Ibuprofen	44	0.99	0.97	1.00
	Diphenhydramine	44	0.94	0.86	0.98
Reference	Ibuprofen	44	0.99	0.98	1.00
	Diphenhydramine	44	0.95	0.90	0.98

Comments on Pharmacokinetic and Statistical Analysis:

The firm's analysis of PK parameters included the data for subjects # 14, 25, 32 and 39 using the test product and subjects # 46, 58, 69, 76 and 83 using the reference product. For all subjects the pre-dose plasma concentration was < 5% of their Cmax. According to the BA/BE Guidance, subjects with a pre-dose concentration value of >5% of Cmax should be excluded from the statistical analysis. The reviewer agrees with the firm's decision to include all subjects for the statistical analysis.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The single-dose fasting bioequivalence study on 1 x 200 mg/ 38 mg tablet is acceptable.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

A. Ibuprofen

Analyte 1					
Time (hr)	Test (n= 44)		Reference (n= 44)		T/R Ratio
	Mean (ng/ mL)	% CV	Mean (ng/ mL)	% CV	
0.00	25.93	334.00	30.03	360.81	0.86
0.17	1242.90	142.03	2129.37	135.98	0.58
0.33	4629.20	86.54	6366.26	102.95	0.73
0.67	10749.50	63.82	11163.29	70.86	0.96
1.00	14045.65	57.10	14795.37	57.62	0.95
1.25	15125.28	51.32	17081.15	47.38	0.89
1.50	15580.59	43.22	17888.87	42.17	0.87
2.00	15374.36	35.66	17313.01	35.86	0.89
2.50	14587.64	35.78	14736.57	32.59	0.99
3.00	12855.61	33.95	12959.23	28.60	0.99
3.50	11024.18	35.27	11240.02	28.20	0.98
4.00	9735.77	31.60	9718.57	31.19	1.00
4.50	9572.55	48.00	8785.70	35.79	1.09
5.00	7282.55	46.37	6788.70	34.59	1.07
6.00	4583.52	41.52	4341.50	35.03	1.06
8.00	2314.17	45.52	2209.16	38.06	1.05
10.00	1276.90	49.00	1227.44	41.63	1.04
12.00	712.19	59.27	688.29	48.87	1.03
16.00	207.02	80.59	197.99	72.95	1.05

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

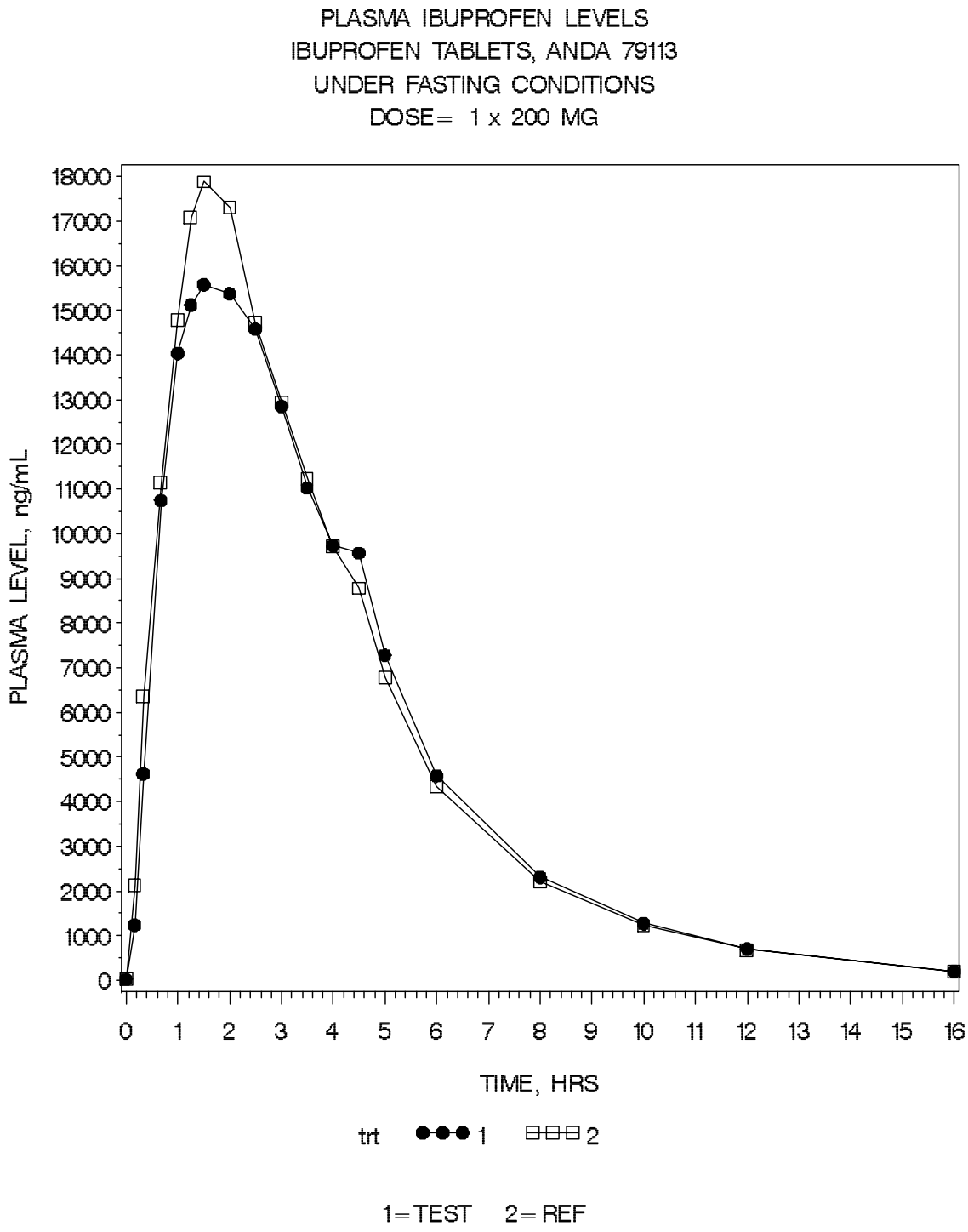
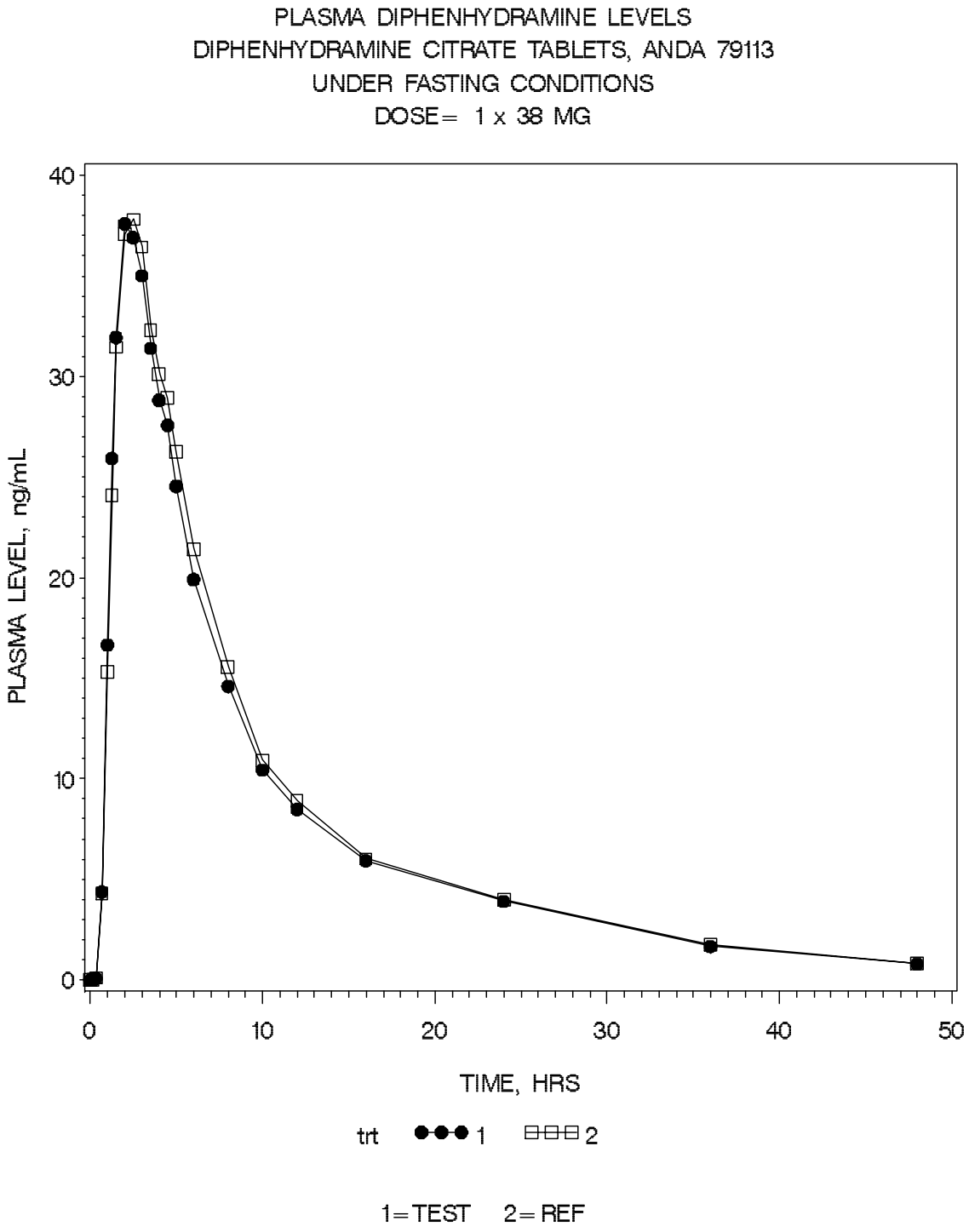


Table 19. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

B. Diphenhydramine

Analyte 1					
Time (hr)	Test (n= 44)		Reference (n= 44)		T/R Ratio
	Mean (ng/ mL)	% CV	Mean (ng/ mL)	% CV	
0.00	0.00	.	0.00	.	.
0.17	0.00	.	0.01	663.32	0.00
0.33	0.10	336.73	0.11	453.13	0.89
0.67	4.39	96.85	4.32	138.72	1.02
1.00	16.66	59.90	15.33	85.89	1.09
1.25	25.94	50.63	24.09	70.68	1.08
1.50	31.96	47.93	31.47	57.23	1.02
2.00	37.60	37.70	37.11	46.19	1.01
2.50	36.92	34.38	37.82	41.30	0.98
3.00	35.02	33.38	36.44	38.28	0.96
3.50	31.42	33.07	32.34	34.21	0.97
4.00	28.82	32.77	30.12	34.94	0.96
4.50	27.59	34.84	28.93	37.02	0.95
5.00	24.55	35.67	26.28	37.44	0.93
6.00	19.91	37.27	21.44	38.06	0.93
8.00	14.60	41.42	15.57	40.62	0.94
10.00	10.44	45.39	10.93	44.30	0.96
12.00	8.48	46.71	8.92	46.55	0.95
16.00	5.94	53.18	6.02	51.84	0.99
24.00	3.91	63.36	4.00	60.55	0.98
36.00	1.66	81.25	1.77	77.47	0.94
48.00	0.80	127.24	0.83	116.07	0.96

Figure 2. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 20. Study Information

A. Ibuprofen

Study Number	R06-0741
Study Title	A Relative Bioavailability Study of 200 mg/38 mg Ibuprofen/Diphenhydramine Citrate Tablets vs. Caplets Under Non-Fasting Conditions
Clinical Site (Name, Address, Phone #)	PRACS Institute, Ltd. 4801 Amber Valley Parkway Fargo, ND 58104 (701) 239-4750
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I: 29 April 2007
	Period II: 6 May 2007
Analytical Site (Name, Address, Phone #)	PRACS Institute, Ltd. 4801 Amber Valley Parkway Fargo, ND 58104 (701) 239-4750
Analysis Dates	June 4, 2007 – June 15, 2007
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	47 days

B. Diphenhydramine

Study Number	R06-0741
Study Title	A Relative Bioavailability Study of 200 mg/38 mg Ibuprofen/Diphenhydramine Citrate Tablets vs. Caplets Under Non-Fasting Conditions
Clinical Site (Name, Address, Phone #)	PRACS Institute, Ltd. 4801 Amber Valley Parkway Fargo, ND 58104 (701) 239-4750
Principal Investigator	Alan K. Copa, Pharm.D.
Dosing Dates	Period I: 29 April 2007
	Period II: 6 May 2007
Analytical Site (Name, Address, Phone #)	PRACS Institute, Ltd. 4801 Amber Valley Parkway Fargo, ND 58104 (701) 239-4750
Analysis Dates	June 8, 2007 – June 19, 2007
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	51 days

Table 21. Product Information

Product	Test		Reference	
Treatment ID	R06-0740 & R06-0741		R06-0740 & R06-0741	
Product Name	Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/ 38 mg		Advil® PM Caplets	
Manufacturer	Perrigo R&D Company		Wyeth Consumers Healthcare	
Batch/Lot No.	7D1728		B59856	
Manufacture Date	04/16/2007		N/A	
Expiration Date	N/A		04/09	
Strength	Ibuprofen: 200 mg Diphenhydramine Citrate: 38 mg		Ibuprofen: 200 mg Diphenhydramine Citrate: 38 mg	
Dosage Form	Tablet (caplet)		Tablet (caplet)	
Bio-batch Size	(b) (4)		N/A	
Production Batch Size			N/A	
Potency	Ibuprofen: (b) (4) Diphenhydramine Citrate: (b) (4)%		Ibuprofen: (b) (4) Diphenhydramine Citrate: (b) (4)%	
Content Uniformity (mean, %CV)	Ibuprofen	Mean: 99.7% RSD: 1.5% AV: 3.6	Ibuprofen	Mean: 102.6% RSD: 1.8% AV: 5.4
	Diphenhydramine Citrate	Mean: 97.2% RSD: 1.5% AV: 4.9	Diphenhydramine Citrate	Mean: 99.2% RSD: 4.5% AV: 10.8
Dose Administered	One tablet per subject per dosing period		One tablet per subject per dosing period	
Route of Administration	Oral		Oral	

Table 22. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	44 subjects enrolled and completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1 group
Washout Period	At least 7 days
Randomization Scheme	AB: 3, 5, 8, 11, 12, 16, 17, 18, 20, 21, 22, 25, 29, 30, 31, 32, 33, 35, 39, 40, 42 and 44 BA: 1, 2, 4, 6, 7, 9, 10, 13, 14, 15, 19, 23, 24, 26, 27, 28, 34, 36, 37, 38, 41 and 43
Blood Sampling Times	Pre-dose (0), 0.167, 0.33, 0.67, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00*, 36.00* and 48.00* hours post-dose
Blood Volume Collected/Sample	One (b) (4) was used to collect for ibuprofen and diphenhydramine. 22 blood samples per period x 2 study periods (total of 44 samples, 440 mL total volume).
Blood Sample Processing/Storage	Samples were collected by (b) (4) The plasma samples for study hours 0.167 through 16 (b) (4) (one for ibuprofen and one for diphenhydramine). The plasma samples for study hour 24 though 48 were (b) (4) (diphenhydramine only). The plasma samples were (b) (4) or colder until shipment for sample analysis.
IRB Approval	Yes, March 28, 2007
Informed Consent	Yes, March 28, 2007
Length of Fasting Before Meal	An overnight fast of at least 10.5 hours. Following consumption of the standardized high-fat and high-calorie breakfast (FDA standard meal), a fast (except water) will be maintained for at least 4 hours after dosing.
Length of Confinement	At least 10.5 hours prior to and until at least 24 hours after dosing each period. Volunteers returned to the clinical site for the 36 hour and 48 hour blood sample.
Safety Monitoring	The subjects were monitored throughout the confinement portion of the study. Blood pressure and heart rate were measured prior to dosing and at 24 hours after each dose.
Standard FDA Meal Used?	Yes

* For diphenhydramine only

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 23. Demographics Profile of Subjects Completing the Bioequivalence Study

A. Ibuprofen

		R06-0741 Treatment Groups	
		Test Product N=44[1]	**Reference Product N=44[1]**
Age (years)	Mean ± SD	28.41 ± 13.91	28.41 ± 13.91
	Range	18 - 75	18 - 75
Age Groups	< 18	-	-
	18 – 39	34 (77.27%)	34 (77.27%)
	40 – 64	9 (20.45%)	9 (20.45%)
	65 – 75	1 (2.27%)	1 (2.27%)
	> 75	-	-
Sex	Male	15 (34.09%)	15 (34.09%)
	Female	29 (65.91%)	29 (65.91%)
Hispanic or Latino Race	N	-	-
	A	-	-
	B	-	-
	I	-	-
	W	2 (4.55%)	2 (4.55%)
Not Hispanic or Latino Race	N	1 (2.27%)	1 (2.27%)
	A	1 (2.27%)	1 (2.27%)
	B	-	-
	I	-	-
	W	40 (90.91%)	40 (90.91%)
BMI	Mean ± SD	25.11 ± 3.26	25.11 ± 3.26
	Range	19.4 - 31.9	19.4 - 31.9
Other Factors			

[1]Subjects used in final statistical report

RACE:

American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W

B. Diphenhydramine

		R06-0741	
		Treatment Groups	
		Test Product N=43[1]	Reference Product N=43[1]
Age (years)	Mean ± SD	28.00 ± 13.81	28.00 ± 13.81
	Range	18 - 75	18 - 75
Age Groups	< 18	-	-
	18 – 39	34 (79.07%)	34 (79.07%)
	40 – 64	8 (18.60%)	8 (18.60%)
	65 – 75	1 (2.33%)	1 (2.33%)
	> 75	-	-
Sex	Male	14 (32.56%)	14 (32.56%)
	Female	29 (67.44%)	29 (67.44%)
Hispanic or Latino Race	N	-	-
	A	-	-
	B	-	-
	I	-	-
	W	2 (4.65%)	2 (4.65%)
Not Hispanic or Latino Race	N	1 (2.33%)	1 (2.33%)
	A	1 (2.33%)	1 (2.33%)
	B	-	-
	I	-	-
	W	39 (90.70%)	39 (90.70%)
BMI	Mean ± SD	24.97 ± 3.15	24.97 ± 3.15
	Range	19.4 - 31.9	19.4 - 31.9
Other Factors			

[1]Subjects used in final statistical report

RACE:

American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W

Table 24. Dropout Information, Fed Bioequivalence Study

R06-0741				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
None	N/A	N/A	N/A	N/A

Table 25. Study Adverse Events, Fed Bioequivalence Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups	
	R06-0741	
	Test N=44[2]	Reference N=44[2]
	n (%)[3]	n (%)[3]
General disorders and administration site conditions		
Hyperhidrosis	1 (2.27%)	-
Vessel puncture site haematoma	1 (2.27%)	-
Nervous system disorders		
Dizziness	2 (4.55%)	-
Headache	1 (2.27%)	-
Total Subjects Reporting at Least One Adverse Event	4 (9.09%)	-

[1] MedDRA Version 9.1
[2] N = Number of subjects dosed for each treatment
[3] n = Number of subjects reporting at least one incidence of respective adverse event;
(%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Table 26. Protocol Deviations, Fed Bioequivalence Study

R06-0741		
Type	Subject #s (Test)	Subject #s (Ref.)
N/A	N/A	N/A

Comments on Adverse Events/Protocol Deviations:

1. No serious adverse events (SAEs) were reported during the fed BE study.

2. Several blood sampling deviations were recorded. The blood sampling time deviations were insignificant.

3. No subject experienced emesis during the fed study.

4.1.2.3 Bioanalytical Results

Table 27. Assay Validation – Within the Fed Bioequivalence Study

A. Ibuprofen

R06-0741 Ibuprofen									
Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	100.0	200.0	500.0	1000	5000	10000	20000	30000	40000
Interday Precision (%CV)	2.6	1.9	2.4	2.7	2.4	2.1	2.4	2.3	3.0
Interday Accuracy (%Deviation)	0.9	-1.1	-1.0	-2.0	0.6	-1.5	3.6	1.8	-1.3
Linearity	0.9977 – 0.9994								
Linearity Range (ng/mL)	100.0 – 40000								
Sensitivity/LOQ (ng/mL)	100.0								

R06-0741 Ibuprofen				
Parameter	**Quality Control Samples**			
Concentration (ng/mL)	300.0	3000	18000	28000
Interday Precision (%CV)	2.7	3.4	2.3	2.3
Interday Accuracy (%Deviation)	-2.4	-2.4	-1.7	-0.9

B. Diphenhydramine

R06-0741
Diphenhydramine

Parameter	**Standard Curve Samples**								
Concentration (ng/mL)	0.5000	1.000	5.000	10.00	50.00	100.0	150.0	175.0	200.0
Interday Precision (%CV)	6.7	5.3	4.3	4.1	3.7	3.8	3.7	3.3	2.8
Interday Accuracy (%Deviation)	-5.8	2.2	0.7	2.4	0.4	-0.3	-0.7	0.2	0.3
Linearity	0.9974 – 0.9996								
Linearity Range (ng/mL)	0.5000 – 200.0								
Sensitivity/LOQ (ng/mL)	0.5000								

R06-0741
Diphenhydramine

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	1.500	20.00	80.00	160.0
Interday Precision (%CV)	9.3	5.7	4.4	4.5
Interday Accuracy (%Deviation)	5.9	6.3	9.0	2.4

Comments on Study Assay Validation:

Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable

Table 28. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
406_05 Version 01	February 19, 2007	Sample Reanalysis and Reporting Criteria

Table 29. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Agree
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

The study assays are acceptable.

4.1.2.4 Pharmacokinetic Results

Table 30. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 34 and Figure 3

A. Ibuprofen

Fed Bioequivalence Study No. R06-0741									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	62311.82	19.38	38245.20	96026.00	65031.28	20.07	38621.10	91397.92	0.96
AUC∞ (hr *ng/ml)	63106.10	19.50	39412.52	98339.00	65870.15	20.10	39298.53	92897.84	0.96
Cmax (ng/ml)	15901.45	24.36	7244.00	27440.00	17065.59	28.25	9361.00	33300.00	0.93
Tmax* (hr)	1.50	.	0.67	4.50	1.75	.	0.67	4.00	0.86
Kel (hr^{-1})	0.32	13.87	0.25	0.48	0.32	14.02	0.24	0.49	1.02
T1/2 (hr)	2.18	12.79	1.46	2.80	2.22	12.71	1.42	2.93	0.98

* Tmax values are presented as median, range

B. Diphenhydramine

Fed Bioequivalence Study No. R06-0741									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	357.22	49.86	118.74	1087.71	401.45	58.76	131.54	1615.25	0.89
AUC∞ (hr *ng/ml)	382.17	53.91	129.56	1266.95	384.26	38.93	141.31	836.74	0.99
Cmax (ng/ml)	40.91	35.47	14.11	77.69	46.41	40.16	18.71	99.78	0.88
Tmax* (hr)	2.50	.	1.50	4.50	2.50	.	1.25	48.00	1.00
Kel (hr^{-1})	0.08	70.36	0.04	0.40	0.08	82.76	0.05	0.50	0.94
T1/2 (hr)	10.34	29.65	1.72	18.40	9.73	24.71	1.38	14.57	1.06

* Tmax values are presented as median, range

Table 31. Geometric Means and 90% Confidence Intervals - Firm Calculated

A. Ibuprofen

IBUPROFEN/DIPHENHYDRAMINE CITRATE TABLETS 200 mg/38 mg (1 x 200 mg/38 mg) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Non-Fasting Bioequivalence Study (R06-0741) N=44[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	61181.42	63721.44	96.01	(93.49, 98.6)
$AUC_{0-\infty}$	61958.52	64540.36	96.00	(93.47, 98.6)
C_{max}	15446.87	16451.19	93.90	(87.6, 100.64)

[1]Geometric means are based on least squares means of ln-transformed values
[2]Subjects used in final statistical report

B. Diphenhydramine

IBUPROFEN/DIPHENHYDRAMINE CITRATE TABLETS 200 mg/38 mg (1 x 200 mg/38 mg) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Non-Fasting Bioequivalence Study (R06-0741) N=43[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	318.10	351.02	90.62	(85.42, 96.14)
$AUC_{0-\infty}$	333.99	363.64	91.85	(86.63, 97.38)
C_{max}	37.57	42.55	88.30	(84.03, 92.78)

[1]Geometric means are based on least squares means of ln-transformed values
[2]Subjects used in final statistical report

Table 32. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

A. Ibuprofen

Ibuprofen/Diphenhydramine Tablets
1 x 200 mg/ 38 mg tablet
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals
Fed Bioequivalence Study No. R06-0741

Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	61181.42	63721.44	0.96	93.49	98.60
AUC∞ (hr *ng/ml)	61958.52	64540.36	0.96	93.47	98.60
Cmax (ng/ml)	15446.87	16451.19	0.94	87.60	100.64

B. Diphenhydramine

Ibuprofen/Diphenhydramine Tablets
1 x 200 mg/ 38 mg tablet
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals
Fed Bioequivalence Study No. R06-0741

Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	318.10	351.02	0.91	85.36	96.20
AUC∞ (hr *ng/ml)	333.99	363.64	0.92	86.31	97.74
Cmax (ng/ml)	37.57	42.55	0.88	83.99	92.83

Table 33. Additional Study Information, Fed Study No. R06-0741

Root mean square error, AUC0-t	0.0742 Ibuprofen 0.1628 Diphenhydramine	
Root mean square error, AUC∞	0.0744 Ibuprofen 0.1607 Diphenhydramine	
Root mean square error, Cmax	0.1935 Ibuprofen 0.1363 Diphenhydramine	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	44 Ibuprofen 42 Diphenhydramine	44 Ibuprofen 41 Diphenhydramine
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0 (Ibuprofen) 2 (Diphenhydramine)	0 (Ibuprofen) 3 (Diphenhydramine)
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞					
Treatment		**n**	**Mean**	**Minimum**	**Maximum**
Test	Ibuprofen	44	0.99	0.96	1.00
	Diphenhydramine	42	0.95	0.86	0.98
Reference	Ibuprofen	44	0.99	0.97	0.99
	Diphenhydramine	41	0.96	0.88	1.00

Comments on Pharmacokinetic and Statistical Analysis:

The firm's analysis of PK parameters did not include the data for subject # 4. The subject's diphenhydramine pre-dose plasma concentration was 5.059 ng/mL. This concentration represented 7 % for subject # 4's Cmax value. This concentration was detected in period 2, possibly as a consequence of a carryover effect from period 1. However, the firm's analysis of PK parameters included the data for subject # 13 using the test product and subjects # 9, 35, 39 using the reference product. For subjects # 13, 9, 35, and 39, the pre-dose plasma concentration was < 5% of their Cmax. According to the BA/BE Guidance, subjects with a pre-dose concentration value of >5% of Cmax should be excluded from the statistical analysis. The reviewer agrees with the firm's decision to exclude subject # 4 and include subjects # 9, 35, 39 for the statistical analysis.

The terminal phases of diphenhydramine could not be adequately estimated for the following subjects: # 6, #13 and #19. Therefore, the pharmacokinetic parameters of AUC infinity, elimination constant and half-life were not calculated for these subjects.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

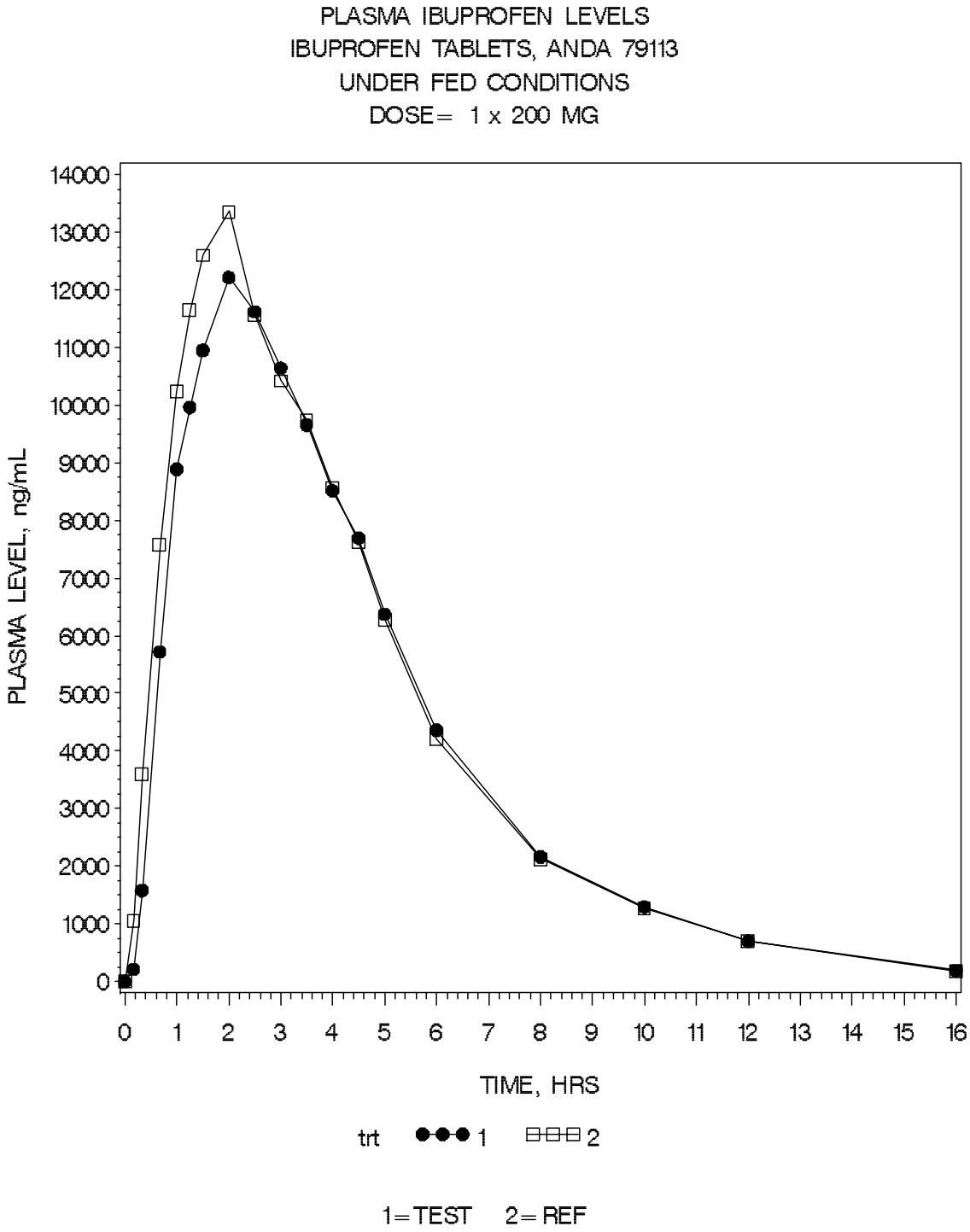
The single-dose fed bioequivalence study on 1 x 200 mg/ 38 mg tablet is acceptable.

Table 34. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

A. Ibuprofen

Analyte 1					
Time (hr)	Test (n= 44)		Reference (n= 44)		T/R Ratio
	Mean (ng/ mL)	% CV	Mean (ng/ mL)	% CV	
0.00	0.00	.	0.00	.	.
0.17	212.30	188.67	1059.44	290.69	0.20
0.33	1581.97	174.62	3608.28	180.00	0.44
0.67	5722.14	113.85	7577.99	105.84	0.76
1.00	8891.87	82.29	10234.73	62.70	0.87
1.25	9966.07	66.44	11656.43	46.88	0.85
1.50	10954.91	49.39	12606.23	41.30	0.87
2.00	12219.07	31.55	13363.08	35.09	0.91
2.50	11626.48	27.69	11577.23	31.91	1.00
3.00	10648.05	30.13	10425.32	26.57	1.02
3.50	9660.52	30.63	9738.48	34.12	0.99
4.00	8519.02	33.16	8574.61	38.03	0.99
4.50	7697.11	36.30	7629.14	40.52	1.01
5.00	6376.84	38.92	6283.52	39.67	1.01
6.00	4362.68	42.81	4208.32	40.99	1.04
8.00	2160.40	50.11	2125.97	49.66	1.02
10.00	1295.38	58.00	1262.52	53.70	1.03
12.00	700.86	64.32	702.40	58.35	1.00
16.00	189.10	84.78	184.69	80.00	1.02

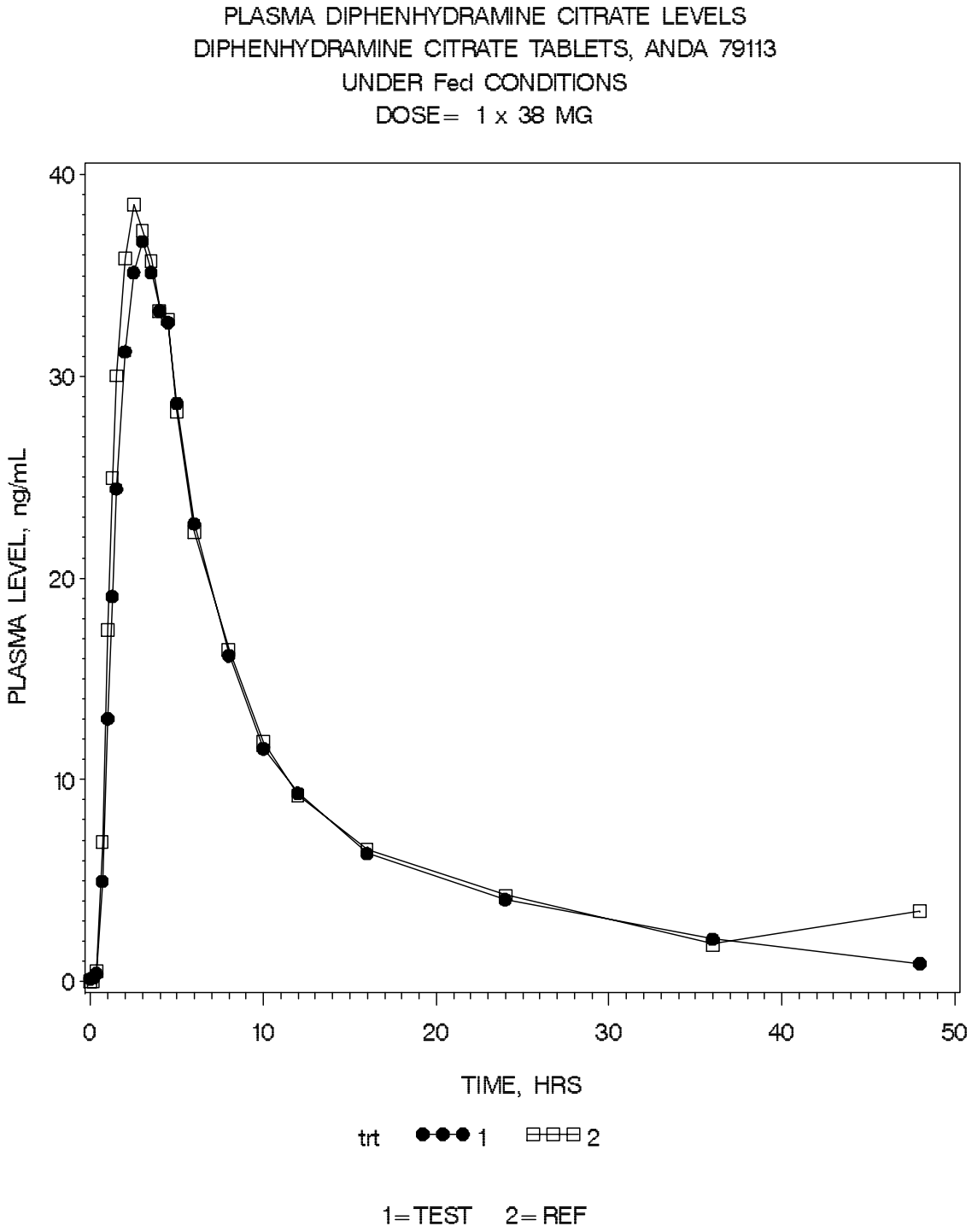
Figure 3. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



B. Diphenhydramine

Analyte 1					
Time (hr)	Test (n= 42)		Reference (n= 41)		T/R Ratio
	Mean (ng/ mL)	% CV	Mean (ng/ mL)	% CV	
0.00	0.13	332.25	0.02	655.74	8.50
0.17	0.18	253.29	0.03	462.60	5.08
0.33	0.40	193.71	0.54	228.59	0.74
0.67	4.97	149.18	6.92	165.22	0.72
1.00	13.04	120.49	17.42	97.52	0.75
1.25	19.10	98.19	24.98	78.69	0.76
1.50	24.43	80.82	30.05	66.84	0.81
2.00	31.23	60.42	35.85	52.22	0.87
2.50	35.16	44.65	38.52	46.42	0.91
3.00	36.70	36.71	37.23	38.88	0.99
3.50	35.15	35.88	35.75	33.85	0.98
4.00	33.25	34.41	33.25	35.31	1.00
4.50	32.67	35.15	32.84	36.18	0.99
5.00	28.67	37.29	28.28	32.65	1.01
6.00	22.69	39.95	22.28	35.52	1.02
8.00	16.16	44.78	16.46	37.86	0.98
10.00	11.55	50.86	11.88	42.59	0.97
12.00	9.34	54.67	9.22	46.71	1.01
16.00	6.34	66.27	6.53	51.67	0.97
24.00	4.06	79.12	4.29	62.84	0.95
36.00	2.10	140.27	1.84	102.39	1.14
48.00	0.89	150.24	3.51	440.02	0.25

Figure 4. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

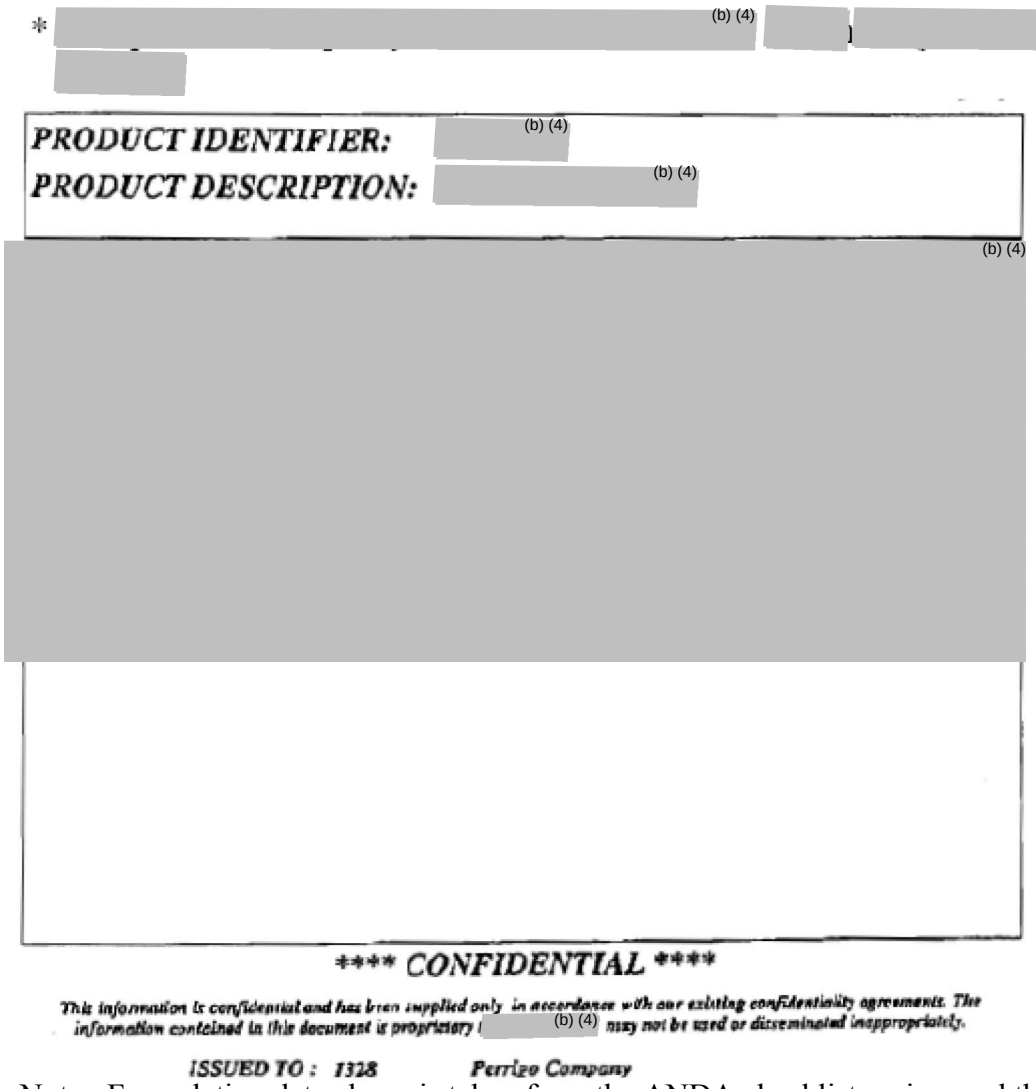


4.2 Formulation Data

Ingredient	Amount (mg) / Tablet	Amount (%)/ Tablet
Cores		
(b) (4)		
Coating		
(b) (4)		
Total		100.00

(b) (4)

SILICON DIOXIDE, COLLOIDAL	(b) (4)
CROSCARMELLOSE SODIUM	
FD&C BLUE NO. 2*	
GLYCERYL BEHENATE	
HYDROXYPROPYL CELLULOSE	
(b) (4) (b) (4)	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
STARCH (b) (4), PREGELATINIZED	
TALC *	
TITANIUM DIOXIDE *	
POLYVINYL ALCOHOL *	
POLYETHYLENE GLYCOL (b) (4)	



Note: Formulation data above is taken from the ANDA checklist review and the IIG limits have been verified by the reviewer.

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	Acceptable

4.3 Dissolution Data

Dissolution Review Path	DFS N 079113 N 000 AB 13-Feb-2008

Table 35. Dissolution Data

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.05M pH 6.5 Phosphate Buffer
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Perrigo Analytical R&D 655, Hooker Rd Plant 4 Allegan, MI-49024	

Study Ref No.	Testing Dates	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)							Study Report Location
						5	10	15	20	30	45	60	
Study Report #:33635 -A	2-05-08 - 2-07-08 (Ibuprofen data)	Test Product PC#050XB\ Lot# 7D1728 Mfg. date: 04/16/07	Ibuprofen 200mg/ Caplet Diphenhydramine Citrate 38mg/Caplet	12	Mean	56	83	93	96	98	98	98	3.2.P. 2.2.1.3
					Range	(b) (4)							
					%CV	10.21	3.50	2.69	2.13	1.94	2.15	1.95	
Study Report #:33635 -A	2-05-08 - 2-07-08 (Diphenhydramine data)	Test Product PC#050XB\ Lot# 7D1728 Mfg. date: 04/16/07	Ibuprofen 200mg/ Caplet Diphenhydramine Citrate 38mg/Caplet	12	Mean	76	89	93	95	95	96	96	3.2.P. 2.2.1.3
					Range	(b) (4)							
					%CV	3.49	2.13	2.06	2.23	2.20	2.19	2.20	
Study Report #:33635 -A	2-05-08 - 2-07-08 (Ibuprofen data)	Reference Product Advil PM Caplet\s Lot#B59856 Exp. Date: 04/09	Ibuprofen 200mg/ Caplet Diphenhydramine Citrate 38mg/Caplet	12	Mean	53	87	98	101	102	103	103	3.2.P. 2.2.1.3
					Range	(b) (4)							
					%CV	8.61	3.12	1.77	1.79	1.83	1.75	1.70	
Study Report #:33635 -A	2-05-08 - 2-07-08 (Diphenhydramine data)	Reference Product Advil PM Caplet\s Lot#B59856 Exp. Date: 04/09	Ibuprofen 200mg/ Caplet Diphenhydramine Citrate 38mg/Caplet	12	Mean	88	97	97	98	98	98	98	3.2.P. 2.2.1.3
					Range	(b) (4)							
					%CV	6.96	4.22	4.18	3.92	3.83	3.96	3.81	

4.4 Detailed Regulatory History (If Applicable)

None

4.5 Consult Reviews

None

4.6 SAS Output

4.6.1 Fasting Study Data (Ibuprofen)

FASTING CONCENTRATION DATASET

(b) (4)

125 pages have been withheld following this page as b5

4.7 Additional Attachments

None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 79-113

APPLICANT: Perrigo R&D Company

DRUG PRODUCT: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg (OTC)

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

We acknowledge that you will conduct dissolution testing using the following FDA-recommended method and specification:

The dissolution testing should be conducted in 900 mL of 50 mM Phosphate buffer, pH 6.5, at 37°C ± 0.5°C using USP apparatus 2 (paddle) at 50 rpm.

The test product should meet the following specification:

NLT (b) (4) (Q) of both drug components in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

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

4.8 Outcome Page

ANDA: 79-113

5 *COMPLETED ASSIGNMENT FOR 79113 ID: 5742*

Reviewer: Johnson, Glendolynn **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Ibuprofen/ Diphenhydramine Tablets

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5742	8/17/2007	Bioequivalence Study	Fasting Study	1	1
5742	8/17/2007	Bioequivalence Study	Fed Study	1	1
				Bean Total:	2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Glendolynn S Johnson
6/26/2008 11:21:54 AM
BIOPHARMACEUTICS

Yih Chain Huang
6/26/2008 11:25:41 AM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
6/26/2008 11:46:00 AM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	79-113	
Drug Product Name	Ibuprofen/Diphenhydramine Citrate Tablets	
Strength (s)	200 mg/38 mg	
Applicant Name	Perrigo R&D Company	
Address	515 Eastern Avenue, Allegen, MI 49010	
Applicant's Point of Contact	Valerie Gallagher, Associate Director, Reg. Affairs	
Contact's Phone Number	269-673-8451	
Contact's Fax Number	269-673-7655	
Submission Date(s)	17 Aug 2007	
Amendment Date(s)	13 Feb 2008	
First Generic	Yes	
Reviewer	April C. Braddy, Ph.D.	
Study Number (s)	R06-0740	R06-0741
Study Type (s)	Fasting (STF)	Fed (STP)
Strength(s)	200 mg/38 mg	200 mg/38 mg
Clinical Site	PRACS Institute, Ltd.	
Clinical Site Address	4801 Amber Valley Parkway, Fargo, ND 58104	
Analytical Site	PRACS Institute, Ltd.	
Analytical Address	4801 Amber Valley Parkway, Fargo, ND 58104	
OUTCOME DECISION	INCOMPLETE	

I. EXECUTIVE SUMMARY

This is a review of the dissolution amendment only.

There is no USP method for this product but there is an FDA-recommended method. The firm's dissolution testing with the FDA-recommended method are acceptable at the S_1 level. However, the firm's proposed specification of NLT (b) (4) minutes is not the FDA-recommended specification [**NLT** (b) (4) **(Q) in 30 minutes**] for both drug components (ibuprofen and diphenydramine). The firm should acknowledge the FDA-recommended method and specification.

The DBE will review the fasted and fed BE studies at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☒	☐	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☒	☐	☐
Is FDA method in the public dissolution database (on the web)			☐	☒	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☒	☐	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.05M pH 6.5 Phosphate Buffer
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Dissolution Testing Site (Name, Address)	Perrigo Analytical R&D 655, Hooker Rd Plant 4 Allegan, MI-49024	

Study Ref No.	Testing Dates	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)							Study Report Location
						5	10	15	20	30	45	60	
Study Report #:33635-A	2-05-08 - 2-07-08 (Ibuprofen data)	Test Product PC#050XB\ Lot# 7D1728 Mfg. date: 04/16/07	Ibuprofen 200mg/ Caplet Diphenhydramine Citrate 38mg/Caplet	12	Mean	56	83	93	96	98	98	98	3.2.P. 2.2.1.3
					Range	(b) (4)							
					%CV	10.21	3.50	2.69	2.13	1.94	2.15	1.95	
Study Report #:33635-A	2-05-08 - 2-07-08 (Diphenhydramine data)	Test Product PC#050XB\ Lot# 7D1728 Mfg. date: 04/16/07	Ibuprofen 200mg/ Caplet Diphenhydramine Citrate 38mg/Caplet	12	Mean	76	89	93	95	95	96	96	3.2.P. 2.2.1.3
					Range	(b) (4)							
					%CV	3.49	2.13	2.06	2.23	2.20	2.19	2.20	
Study Report #:33635-A	2-05-08 - 2-07-08 (Ibuprofen data)	Reference Product Advil PM Caplet\s Lot#B59856 Exp. Date: 04/09	Ibuprofen 200mg/ Caplet Diphenhydramine Citrate 38mg/Caplet	12	Mean	53	87	98	101	102	103	103	3.2.P. 2.2.1.3
					Range	(b) (4)							
					%CV	8.61	3.12	1.77	1.79	1.83	1.75	1.70	
Study Report #:33635-A	2-05-08 - 2-07-08 (Diphenhydramine data)	Reference Product Advil PM Caplet\s Lot#B59856 Exp. Date: 04/09	Ibuprofen 200mg/ Caplet Diphenhydramine Citrate 38mg/Caplet	12	Mean	88	97	97	98	98	98	98	3.2.P. 2.2.1.3
					Range	(b) (4)							
					%CV	6.96	4.22	4.18	3.92	3.83	3.96	3.81	

II. COMMENTS:

1. Currently, there is no USP method for Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg. The dissolution method and specification for the over-the-counter product, Advil® PM Caplets® (Ibuprofen, 200 mg/Diphenhydramine Citrate, 38 mg) are proposed by the innovator firm, Wyeth Consumer Healthcare.

(NOT TO BE RELEASED UNDER FOIA)

Location of NDA Dissolution Review	Internal database: Division of System Files v 2.0. NDA 021394 Review Clin Pharm Rev if Submiss Biopharmaceutics N 021394 N 000 BB 01-Nov-2005.
Source of Method (USP, FDA or Firm)	FDA (021394)
Medium	50 mM Phosphate buffer, pH 6.5
Volume (mL)	900
USP Apparatus type	II (Paddle)
Rotation (rpm)	50
Dissolution specification	Not less than (NLT) (b) (4) (Q) in 30 minutes (both drug components)

2. The firm's dissolution testing on its Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg, lot # 7D1728 and the reference product, Advil® PM Caplets® (Ibuprofen, 200 mg/Diphenhydramine Citrate, 38 mg), lot # B59856 using the FDA-recommended method is acceptable.

3. The firm proposed a specification of NLT (b) (4) minutes for both drug components) which differs from the FDA-recommended specification of NLT (b) (4) (Q) in 30 minutes. However, the firm's test product still met the FDA recommended specification at the S_1 level.

4. As stated in the original review of the dissolution testing data, the firm submitted the SAS datasets, the sixteen (16) bioequivalence (BE) summary tables and sufficient long-term stability data.

5. No Division of Scientific Investigations (DSI) inspections are pending or necessary.

III. DEFICIENCY COMMENT:

1. The firm's proposed specification is not acceptable. The firm should acknowledge and accept the FDA-recommended method and specification for its test product, Ibuprofen/Diphenhydramine Citrate Tablets:

Medium:	50 mM Phosphate buffer, pH 6.5
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle)
Rotational Speed:	50 rpm
Specification:	**NLT (b) (4) (Q) in 30 minutes for ibuprofen and diphendydramine**

IV. RECOMMENDATION:

1. The *in vitro* dissolution testing conducted by Perrigo R&D Company, Inc., on its Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg, lot # 7D1728 is acceptable.

2. The firm should acknowledge and accept the FDA-recommended dissolution method and specification for its test product, Ibuprofen/Diphenhydramine Citrate Tablets.

The firm should be informed of the above deficiency comment and recommendations.

V. DISSOLUTION CONSULT

From: Seo, Paul
Sent: Thursday, February 28, 2008 10:26 AM
To: Braddy, April
Cc: Seo, Paul
Subject: RE: Dissolution Consult: ANDA 79-113 Ibuprofen and Diphenhydramine Citrate Tablets - Perrigo

Hi April,

The firm's dissolution method/data is already very fast (and minimally discriminating) as it is, so I see no reason to grant a specification of (b) (4) for them. I concur that the firm should acknowledge the DBE recommended specs of (b) (4)/30.

Thanks,
Paul

From: Braddy, April
Sent: Thursday, February 28, 2008 10:23 AM
To: Seo, Paul
Subject: Dissolution Consult: ANDA 79-113 Ibuprofen and Diphenhydramine Citrate Tablets - Perrigo

Good morning, Paul:

As per our discussion, the firm's proposed specification of NLT (b) (4) minutes is not acceptable. Based on the submitted dissolution testing data, the firm's test product meets the FDA-recommended specification [NLT (b) (4) (Q) in 30 min] at the S1 level for both drug components (ibuprofen and diphenydramine). Therefore, it will be requested that the firm acknowledge and accept the FDA-recommended method and specification for Ibuprofen and Diphenhydramine Citrate Tablets.

Sincerely,

April

April C. Braddy, Ph.D.
Pharmacologist
FDA/CDER/OPS/OGD/DBE
PH 240-276-8782
Fax 240-276-8794
april.braddy@fda.hhs.gov

BIOEQUIVALENCE DEFICIENCY

ANDA: 79-113

APPLICANT: Perrigo R&D Company

DRUG PRODUCT: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg

The Division of Bioequivalence has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiency has been identified:

Based on the dissolution testing data you submitted for Ibuprofen/Diphenydramine Citrate Tablets, your proposed specification of not less than (NLT) (b) (4) minutes is not acceptable. Therefore, please provide acknowledgement for your acceptance of the following FDA-recommended dissolution method and specification:

Medium:	50 mM Phosphate Buffer, pH 6.5
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle)
Rotational Speed:	50 rpm

The test product should meet the following specification:

NLT (b) (4) **(Q)** of the labeled amount of ibuprofen and diphenhydramine in the dosage form should be dissolved in **30 minutes**.

Sincerely yours,

{See appended electronic signature page}

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

VI. OUTCOME

ANDA: 79-113

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
4935	2/13/2008	Dissolution Data	Dissolution Amendment	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

April Braddy
2/28/2008 03:16:14 PM
BIOPHARMACEUTICS

Moheb H. Makary
2/28/2008 03:22:12 PM
BIOPHARMACEUTICS

Barbara Davit
2/29/2008 05:10:03 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	79-113	
Drug Product Name	Ibuprofen/Diphenhydramine Citrate Tablets	
Strength (s)	200 mg/38 mg	
Applicant Name	Perrigo R&D Company	
Address	515 Eastern Avenue, Allegen, MI 49010	
Applicant's Point of Contact	Valerie Gallagher, Associate Director, Reg. Affairs	
Contact's Phone Number	269-673-8451	
Contact's Fax Number	269-673-7655	
Submission Date(s)	17 Aug 2007	
First Generic	Yes	
Reviewer	April C. Braddy, Ph.D.	
Study Number (s)	R06-0740	R06-0741
Study Type (s)	Fasting (STF)	Fed (STP)
Strength(s)	200 mg/38 mg	200 mg/38 mg
Clinical Site	PRACS Institute, Ltd.	
Clinical Site Address	4801 Amber Valley Parkway, Fargo, ND 58104	
Analytical Site	PRACS Institute, Ltd.	
Analytical Address	4801 Amber Valley Parkway, Fargo, ND 58104	
OUTCOME DECISION	INCOMPLETE	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm conducted dissolution testing using its proposed dissolution method. Therefore, the firm should conduct and submit dissolution testing on twelve (12) dosage units of each test and reference product using the following FDA-recommended method: USP Apparatus II (Paddle) @ 50 rpm in 50 mM Phosphate buffer, pH 6.5 (900 mL) at 37˚C ± 0.5˚C.

The DBE will review the fasted and fed BE studies at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☒	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☐	☒	☐
Did the firm conduct dissolution testing with its own proposed method			☒	☐	☐
Is FDA method in the public dissolution database (on the web)			☐	☒	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☒	☐	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	0.05M pH 7.2 Phosphate Buffer
	Volume:	900 mL
	Temperature:	37 ± 0.5 °C
Firm's Proposed Specifications	NLT (b) (4) minutes	
Dissolution Testing Site (Name, Address)	Perrigo Analytical R&D 655, Hooker Rd Plant 4 Allegan, MI-49024	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 5	10	15	20	30	45	60	Study Report Location
Study Report #:32454	04-26-07	Test Product PC#050XB\ Lot# 7D1728 Mfg. date: 04/16/07	Ibuprofen 200mg/ Caplet Diphenhydramine Citrate 38mg/Caplet	12	Mean	68	96	99	100	99	99	99	Perrigo Plant 4 Analytical R&D
					Range	(b) (4)							
					%CV	15.7	2.4	1.8	1.7	1.7	1.8	1.4	
Study Report #:32454	04-26-07	Reference Product Advil PM Caplet\s Lot#B59856 Exp. Date: 04/09	Ibuprofen 200mg/ Caplet Diphenhydramine Citrate 38mg/Caplet	12	Mean	78	101	103	104	104	104	104	
					Range	(b) (4)							
					%CV	8.0	1.7	1.6	1.8	1.8	1.8	1.7	

II. COMMENTS:

1. Currently, there is no USP method for Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg. The dissolution method and specification for the over-the-counter product, Advil® PM Caplets® (Ibuprofen, 200 mg/Diphenhydramine Citrate, 38 mg) are proposed by the innovator firm, Wyeth Consumer Healthcare.

(NOT TO BE RELEASED UNDER FOIA)

Location of NDA Dissolution Review	Internal database: Division of System Files v 2.0. NDA 021394 Review Clin Pharm Rev if Submiss Biopharmaceutics N 021394 N 000 BB 01-Nov-2005.
Source of Method (USP, FDA or Firm)	FDA (021394)
Medium	50 mM Phosphate buffer, pH 6.5
Volume (mL)	900
USP Apparatus type	II (Paddle)
Rotation (rpm)	50
Dissolution specification	Not less than (NLT) (b) (4)(Q) in 30 minutes

2. The firm's dissolution testing on its Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg, lot # 7D1728 and the reference product, Advil® PM Caplets® (Ibuprofen, 200 mg/Diphenhydramine Citrate, 38 mg), lot # B59856 using its proposed method is not acceptable, see Table 2. The firm should conduct dissolution testing using the FDA-recommended dissolution method.

3. The firm provided the SAS datasets (.xpt format) for its bioequivalence (BE) studies.

4. The firm provided the sixteen (16) BE summary tables in pdf and/or word format.

5. The long-term stability data provided by the firm is sufficient to cover the maximum storage time for the human plasma samples for both of its BE studies.

6. No Division of Scientific Investigations (DSI) inspections are pending or necessary.

III. DEFICIENCY COMMENT:

1. The firm did not conduct its dissolution testing using the FDA-recommended dissolution method. The FDA-recommended dissolution method is as follows:

Medium:	50 mM Phosphate buffer, pH 6.5
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle)
Rotational Speed:	50 rpm
Sampling times:	10, 15, 20, and 30 minutes for both drug components

IV. RECOMMENDATION:

1. The *in vitro* dissolution testing conducted by Perrigo R&D Company, Inc., on its Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg, lot # 7D1728 is incomplete due to the reason provide in deficiency comment No. 1.

   The firm should conduct and submit dissolution testing on twelve (12) dosage units of each test and reference product using the following FDA-recommended dissolution method:

Medium:	50 mM Phosphate buffer, pH 6.5
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle)
Rotational Speed:	50 rpm
Sampling times:	10, 15, 20, and 30 minutes for both drug components

The firm should be informed of the above deficiency comment and recommendation

BIOEQUIVALENCE DEFICIENCY

ANDA: 79-113

APPLICANT: Perrigo R&D Company

DRUG PRODUCT: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg

The Division of Bioequivalence has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiencies have been identified:

Your dissolution testing is incomplete. Please submit dissolution testing on twelve (12) dosage units of each test and reference product (**both drug components)** using the following FDA-recommended method:

Medium:	50 mM Phosphate Buffer, pH 6.5
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle)
Rotational Speed:	50 rpm
Sampling times:	10, 15, 20, and 30 minutes for **both drug components**

Please submit the comparative dissolution results which should include the individual tablet data as well as the mean, range, %CV at each time point for the 12 tablets tested and dates of dissolution testing. In addition, please submit the dissolution testing data summary table with the above data.

Sincerely yours,

{See appended electronic signature page}

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

V. OUTCOME

ANDA: 79-113

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
4576	8/17/2007	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

April Braddy
1/28/2008 08:44:03 AM
BIOPHARMACEUTICS

Moheb H. Makary
1/28/2008 08:46:16 AM
BIOPHARMACEUTICS

Barbara Davit
1/31/2008 03:36:55 PM
BIOPHARMACEUTICS

BIOEQUIVALENCE CHECKLIST
for Application Completeness of First Generic ANDA

ANDA# 79-113 **FIRM NAME Perrigo Company**

DRUG NAME Ibuprofen/Diphenhydramine Citrate Tablets

DOSAGE FORM 200 mg/38 mg
SUBJ: Request for examination of:

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☒	**Waiver does NOT meet statutory requirements**
	Reason: N/A

RECOMMENDATION: Complete

Reviewed by:

Zakaria Z. Wahba, Ph.D. Date: _____
Reviewer

Chandra S. Chaurasia, Ph.D. Date: _____
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments/ Information to Request
Protocol	☒	☐	2	2	Fasting and fed studies
Assay Methodology	☒	☐	1	1	LC/MS/MS method
Procedure SOP	☒	☐	1	1	
Methods Validation	☒	☐	1	1	
Study Results Ln/Lin	☒	☐	2	2	
Adverse Events	☒	☐	2	2	
IRB Approval	☒	☐	2	2	
Dissolution Data	☒	☐	1	1	
Pre-screening of Patients	☒	☐	2	2	
Chromatograms	☒	☐	2	2	
Consent Forms	☒	☐	2	2	
Composition	☒	☐	1	1	
Summary of Study	☒	☐	2	2	
Individual Data & Graphs, Linear & Ln	☒	☐	2	2	
PK/PD Data Disk Submitted)	☒	☐	2	2	
Randomization Schedule	☒	☐	2	2	
Protocol Deviations	☒	☐	2	2	
Clinical Site	☒	☐			same for fasting and fed studies
Analytical Site	☒	☐			same for fasting and fed studies

Item Verified:	**YES**	**NO**			**Comments/** **Information to Request**
Medical Records	☒	☐	2	2	
Clinical Raw Data	☒	☐	2	2	
Test Article Inventory	☒	☐			Not provided in the bioequivalence section of ANDA
BIO Batch Size	☒	☐	1	1	same lot for fasting and fed studies
Assay of Active Content Drug	☒	☐	2	2	Test and reference
Content Uniformity	☒	☐	1	1	Test
Date of Manufacture	☒	☐			
Exp. Date of RLD	☒	☐			
BioStudy Lot Numbers	☒	☐	1	1	same lot for fasting and fed studies
Statistics	☒	☐	2	2	
Summary results provided by the firm indicate studies pass BE criteria	☒	☐	2	2	
Waiver requests for other strengths / supporting data	☐	☒			N/A

Additional Comments regarding the ANDA:

1. The RLD is Advil® PM (Diphenhydramine Citrate; Ibuprofen) Tablets, 38MG;200MG (NDA 021394, Approval Date: Dec 21, 2005).

2. The DBE current recommendations for this drug are provided in the following control document response to Perrigo Company.

Perrigo Company
Attention: David Kloosterman
515 Eastern Avenue
Allegan, Michigan 49010

SEP 2 1 2007

Reference Number: OGD #06-0321

Dear Mr. Kloosterman:

This letter is in response to your correspondence dated March 06, 2006. You request that the Office of Generic Drugs (OGD) provide bioequivalence recommendations regarding Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg. OGD provides the following comments:

1. The following study is recommended to establish bioequivalence of Ibuprofen and Diphenhydramine Tablets:

   A single-dose fasting in-vivo bioequivalence study comparing Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg, to the reference listed drug (RLD), Advil PM®, (Ibuprofen and Diphenhydramine Citrate) Tablets, 200 mg/38 mg.

2. Please measure only the parent compounds, ibuprofen and diphenhydramine.

3. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the following method:

Apparatus:	USP Apparatus II (paddle)
Speed:	50 rpm
Medium:	50 mM phosphate buffer, pH 6.5
Volume:	900 mL
Sampling Times:	10, 15, 20, 30 minutes and until at least (b) (4) of the labeled content is dissolved.

4. Please provide a table that identifies every missing sample in the study. Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis. Please provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for identifying and reassaying pharmacokinetically anomalous samples. The SOP(s)

should clearly state objective criteria for defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study; otherwise, the Division of Bioequivalence may not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.

5. The bioequivalence data to be submitted in an ANDA should be provided in a diskette or CD in SAS Transport format in two separate files as described below:

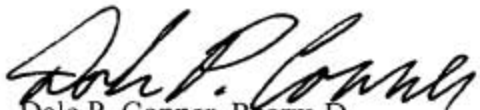
   a. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf
   b. SUBJ SEQ PER TRT C1 C2 C3 ..... Cn

   Please separate each field with a blank space and indicate missing values with a period (.).

   The eCTD is the preferred format for electronic submission to CDER. The eCTD format applies to ANDAs. For more information on eCTD, and to view the eCTD Guidance, please see http://www.fda.gov/cder/regulatory/ersr/ectd.htm.

If you have any questions, please call Aaron Sigler, Pharm.D., Project Manager, Division of Bioequivalence at 240-276-8782. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,



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

Completed Assignment for 79113 ID: 663

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
663	8/17/2007	Paragraph 4	Paragraph 4 Checklist	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chandra S. Chaurasia
10/18/2007 08:18:06 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 79-113

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 79-113 Applicant Perrigo R & D Company
Drug Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg Strength(s)

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 12 DEC 2008 Date _____
Chief, Reg. Support Branch Initials MHS Initials _____
Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = _____ NDA# _____
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked _____
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 8/20/2007, BOS=Advil PM NDA 21394, no relevant patent cert provided, NC expires on 12/21/2008. ANDA ack for filing on 8/20/2007(LO dated 12/19/2007). ANDA secured TA on 10/27/2008. ANDA is eligible for Full Approval upon the expiration of NC exclusivity which protects NDA 21394. This date is 12/21/2008.

2. Project Manager, Dat Doan Team1 Date 7/22/08 Date _____
Review Support Branch Initials dd Initials _____

Original Rec'd date 8/17/07
Date Acceptable for Filing 8/20/07
Patent Certification (type)
Date Patent/Exclus.expires 12/21/08
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio review tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 1/10/08
Date of Office Bio Review 6/26/08
Date of Labeling Approv. Sum 7/16/08
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☒ Date 10/27/08
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date _____ Date _____
Name/Initials _____ Name/Initials _____

Comments:
From: Grace, John F
Sent: Thursday, December 11, 2008 3:09 PM
To: Barlow, James T; Doan, Dat
Subject: RE: 79-113/Perrigo/Diphenhydramine & Ibuprofen

concur

From: Barlow, James T

Sent: Thursday, December 11, 2008 3:07 PM
To: Doan, Dat; Grace, John F
Subject: RE: 79-113/Perrigo/Diphenhydramine & Ibuprofen

I checked Drugs@FDA,OB and USP.
The labeling AP summary signed by John Grace on 7/17/08 remains acceptable.

From: Doan, Dat
Sent: Thursday, December 11, 2008 3:04 PM
To: Barlow, James T; Grace, John F
Subject: 79-113/Perrigo/Diphenhydramine & Ibuprofen

HI John, Jim:

Can I please get your endorsement for ANDA 79-113/Perrigo/Diphenhydramine & Ibuprofen?

<< File: 79113.ap.labeling.summary.pdf >>

<< File: 79113.ap.letter.DOC >>

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date _____
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials _____
Comments:

5. Div. Dir./Deputy Dir. Date 12/15/08
Chemistry Div. I II OR III Initials RMP
Comments: Satisfactory for AP since it was TAed before after the first generic audit. Now has been updated with respected to USP <467> requirement.

6. Frank Holcombe **First Generics Only** Date _____
Assoc. Dir. For Chemistry Initials _____
Comments: (First generic drug review)

7. Vacant Date _____
Deputy Dir., DLPS Initials _____

8. Peter Rickman Date 12/22/08
Director, DLPS Initials wpr
Para.IV Patent Cert: Yes☐ No☒;Pending Legal Action: Yes ☐No ☒;Petition: Yes☐ No☒
Comments:no relevant patents; New Combo Exclusivity expires 12/21/2008; Labeling acceptable 7/16/2008 per AP Summary; Bio acceptable 6/26/2008; EER acceptable 1/10/2008.

Okay for Full Approval when NC exclusivity expires 12/21/08

OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Dat Doan Date12/22/08
Review Support Branch Initials ES

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
4:00pm Time notified of approval by phone
4:20pm Time approval letter faxed

FDA Notification:
12/22/08Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
12/22/08Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

COMIS TABLE:

ORANGE BOOK PRINT OFF:

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/s/

Dat Doan

12/29/2008 11:15:14 AM

OGD APPROVAL ROUTING SUMMARY

ANDA # 79-113 Applicant Perrigo R & D Company
Drug Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg Strength(s)

APPROVAL ☐ TENTATIVE APPROVAL ☒ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date 24 July 2008 Initials MHS	Date _____ Initials _____

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = _____ NDA# _____
Date Checked _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Tentative Approval
Comments: ANDA submitted on 8/20/2007, BOS=Advil PM NDA 21-394, No relevant patent cert, NC exclusivity expires on 12/21/2008. ANDA ack for filing on 8/20/2007(LO dated 12/19/2007). This ANDA is eligible for TA only due to unexpired NC exclusivity

2. Project Manager, Dat Doan Team1 Review Support Branch	Date 7/22/08 Initials dd	Date _____ Initials _____

Original Rec'd date 8/17/07
Date Acceptable for Filing 8/20/07
Patent Certification (type)
Date Patent/Exclus.expires 12/21/08
Citizens' Petition/Legal Case Yes ☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 1/10/08
Date of Office Bio Review 6/26/08
Date of Labeling Approv. Sum 7/16/08
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Acceptable Bio review tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement

Reviewer:	Labeling Team Leader:
Date _____	Date _____
Name/Initials _____	Name/Initials _____

Comments:
From: Grace, John F
Sent: Wednesday, July 23, 2008 2:29 PM
To: Barlow, James T; Doan, Dat
Subject: RE: 79-113/Perrigo/Ibuprofen and Diphenhydramine

concur

From: Barlow, James T
Sent: Wednesday, July 23, 2008 2:28 PM

To: Doan, Dat; Grace, John F
Subject: RE: 79-113/Perrigo/Ibuprofen and Diphenhydramine

I checked Drugs@FDA,OB and USP.
The labeling Approval Summary signed by John Grace on 7/17/08 remains acceptable.

From: Doan, Dat
Sent: Wednesday, July 23, 2008 2:27 PM
To: Barlow, James T; Grace, John F
Subject: 79-113/Perrigo/Ibuprofen and Diphenhydramine

HI John, Jim:

Can I please get your endorsement for ANDA 79-113/Perrigo/Ibuprofen and Diphenhydramine? This is for a TA.

<< File: 79113.ap.labeling.summary.pdf >>
<< File: 79113.ta.letter.DOC >>

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date _____
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials_____
Comments:

5. Div. Dir./Deputy Dir. Date7/29/08
Chemistry Div. I II OR III Initials RMP
Comments:The DP fails to meet USP <467> requirements. Therefore, only a TA letter may be issued.

6. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)

7. Vacant Date_____
Deputy Dir., DLPS Initials_____

8. Peter Rickman Date10/27/08
Director, DLPS Initialswpr
Para.IV Patent Cert: Yes☐ No☒;Pending Legal Action: Yes ☐No ☒;Petition: Yes☐ No☒
Comments:No patents; NC (new combo) Exclusivity expires 12/21/2008; Labeling acceptable 7/16/2008 per AP Summary; Bio acceptable 6/26/2008; EER acceptable 1/10/2008.

TA due to unexpired NC Exclusivity (12/21/08)

OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Dat Doan Date10/27
Review Support Branch Initials se for

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
11:13Time notified of approval by phone
11:15amTime approval letter faxed

FDA Notification:
10/27/08 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
1-/27/08 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

COMIS TABLE:

ORANGE BOOK PRINT OFF:

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/s/

Simon Eng

10/27/2008 11:20:00 AM

Telephone Fax

ANDA 79-113

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8979

TO: Perrigo R & D Company

TEL: (269) 673-8451

ATTN: Valerie Gallagher

FROM: Jim Barlow (Labeling Reviewer)

FAX: (269) 673-7655

:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for (Ibuprofen and Diphenhydramine Citrate Tablets)

).

Pages (including cover): _3_

SPECIAL INSTRUCTIONS:

Labeling Comments

james.barlow@fda.hhs.gov

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	79-113
Date of Submission:	August 17, 2007
Applicant's Name:	Perrigo R&D Company.
Established Name:	Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

---

Labeling Deficiencies:

1. **CONTAINER – Bottles 20 and 500**
   Front Panel: Revise to read as follows – Relocate the "20" and include "Coated"

   Ibuprofen, 200 mg/Diphenhydramine citrate, 38 mg Caplets**

   20 Coated **Capsule-shaped Tablets

2. **CARTON – (20 count container only)**
   Satisfactory in **final print** as of the August 17, 2007 electronic submission

(b) (4)

Submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John Grace
5/15/2008 11:38:34 AM
for Wm Peter Rickman

BIOEQUIVALENCY AMENDMENT

ANDA 79-113

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Perrigo R & D Company TEL: 269-673-8451

ATTN: Valerie Gallagher FAX: 269-673-7655

FROM: Aaron Sigler PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on August 17, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg.

Reference is also made to your amendment dated February 13, 2008.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY

ANDA: 79-113

APPLICANT: Perrigo R&D Company

DRUG PRODUCT: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg

The Division of Bioequivalence has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiency has been identified:

Based on the dissolution testing data you submitted for Ibuprofen/Diphenydramine Citrate Tablets, your proposed specification of not less than (NLT) [redacted] (b) (4) minutes is not acceptable. Therefore, please provide acknowledgement for your acceptance of the following FDA-recommended dissolution method and specification:

Medium:	50 mM Phosphate Buffer, pH 6.5
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle)
Rotational Speed:	50 rpm

The test product should meet the following specification:

NLT (b) (4) (Q) of the labeled amount of ibuprofen and diphenhydramine in the dosage form should be dissolved in **30 minutes**.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Barbara Davit
3/18/2008 06:11:14 PM
Signing for Dale P Conner

MINOR AMENDMENT

ANDA 79-113

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Perrigo R & D Company TEL: 269-673-8451

ATTN: Valerie Gallagher FAX: 269-673-7655

FROM: Dat Doan PROJECT MANAGER: (240) 276-8573

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 17, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg.

SPECIAL INSTRUCTIONS: please see attached

Please submit your response in electronic format. This will improve document availability to review staff.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachment (__**1**__ page). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 79-113 APPLICANT: Perrigo R&D Company

a) DRUG PRODUCT: Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/ 38 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please reduce the drug product release and stability total impurities (Degradants) limit to be more consistent with the reported data. Also, please establish one total limit combined for Ibuprofen and Diphenhydramine instead of two different limits.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The bioequivalence information which you have provided is under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

2. The labeling portion of your application is currently under review. The Division of Labeling and Program Support will notify you, under separate cover, of all labeling deficiencies.

3. If necessary, the drug product release and stability dissolution specifications may require revision according to recommendations of the Division of Bioequivalence. Please note that if the recommended dissolution test method differs from your initially proposed test method, we will request additional information including stability.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Rosario DCosta

3/4/2008 02:51:20 PM

BIOEQUIVALENCY AMENDMENT

ANDA 79-113

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Perrigo R & D Company TEL: 269-673-8451

ATTN: Valerie Gallagher FAX: 269-673-7655

FROM: Aaron Sigler PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on August 17, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ibuprofen / Diphenhydramine Citrate Tablets, 200 mg/38 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY

ANDA: 79-113

APPLICANT: Perrigo R&D Company

DRUG PRODUCT: Ibuprofen/Diphenhydramine Citrate Tablets, 200 mg/38 mg

The Division of Bioequivalence has completed its review of only the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence (BE) studies will be conducted later. The following deficiencies have been identified:

Your dissolution testing is incomplete. Please submit dissolution testing on twelve (12) dosage units of each test and reference product (**both drug components**) using the following FDA-recommended method:

Medium:	50 mM Phosphate Buffer, pH 6.5
Volume:	900 mL
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle)
Rotational Speed:	50 rpm
Sampling times:	10, 15, 20, and 30 minutes for **both drug components**

Please submit the comparative dissolution results which should include the individual tablet data as well as the mean, range, %CV at each time point for the 12 tablets tested and dates of dissolution testing. In addition, please submit the dissolution testing data summary table with the above data.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Barbara Davit
2/1/2008 06:10:53 PM
Signing for Dale P Conner

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 79-113

Perrigo R&D Company
Attention: Valerie Gallagher
515 Eastern Avenue
Allegan, MI 49010

Dear Madam:

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 the telephone conversation dated November 20, 2007 and your correspondence dated December 4, 2007.

NAME OF DRUG: Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg

DATE OF APPLICATION: August 17, 2007

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 20, 2007

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:

Dat Doan
Project Manager
240-276-8573

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Martin Shimer
12/19/2007 10:27:09 AM
Signing for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 79-113 **FIRM NAME**: PERRIGO R & D COMPANY

PIV: NO **Electronic or Paper Submission:** ELECTRONIC (ECTD FORMAT)

RELATED APPLICATION(S):

First Generic Product Received? NO

DRUG NAME: IBUPROFEN AND DIPHENHYDRAMINE CITRATE

DOSAGE FORM: TABLETS, 200 MG/38 MG

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

Random Queue: 1

Chem Team Leader: Mueller, Albert PM: Dat Doan Labeling Reviewer: James Barlow

Letter Date: AUGUST 17, 2007 **Received Date**: AUGUST 20, 2007

Comments: EC- 1 YES **On Cards:** YES

Therapeutic Code: 5030300 ACUTE PAIN, NON-OPIOID

Archival copy: ELECTRONIC (ECTD FORMAT) **Sections** I

Review copy: NA E-Media Disposition: YES SENT TO EDR

Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product

(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Kojo Awuah	**Recommendation:**
Date 12/10/07	☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

Called Perrigo on 11/20/07 and left a message for Ms. Valerie Gallagher to provide the following:

1. **Provide a statement clarifying the functions of the outside labs listed in the application.**
2. **Provide a Quantitative Formula for** [redacted] (b) (4)

Fax received on 12/4/07. Hard copies are being sent by mail.

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Contact Person: Valerie Gallagher Phone (269) 673-8451 ext 9367** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) OTC YES	☒
1.2	**Cover Letter** Dated: AUGUST 17, 2007	☒
*	**Table of Contents (paper submission only)** YES (N/A – eCTD)	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) Y	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) YES	☒
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2** **Patent Certification** 1. Patent number(s) NONE 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☒ PII ☐ PIII ☐ PIV ☐ No Relevant Patents ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? NA b. Expiration of Pediatric Exclusivity? NA 4. Exclusivity Statement: YES	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient (IBU – DMF # (b) (4)) (Diphenhydramine – DMF # (b) (4) b. Type III DMF authorization letter(s) for container closure Y 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA	☒
1.12.11	**Basis for Submission** NDA# : 21-394 Ref Listed Drug: ADVIL PM Firm: WYETH CONSUMER HEALTHCARE ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same as the RLD 2. Active ingredients Ibuprofen USP and Diphenhydramine Citrate USP 3. Inactive ingredients OK as per IIG 4. Route of administration Oral 5. Dosage Form Tablet 6. Strength 200 mg/38 mg	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): Electronic, NA	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Y **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained Y **1.14.1.3** 1 package insert (content of labeling) submitted electronically NA ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained NA **1.14.3.3** 1 RLD label and 1 RLD container label Y	☒

MODULE 2
SUMMARIES

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: _X____PDF (archive) __X__ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) _X____ YES _____ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient) Y** **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product Y** **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture Y** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **E-Submission: __Y___PDF (archive) __Y__ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies Y** **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies Y Table 2. Statistical Summary of the Comparative BA Data Y Table 4. Summary of In Vitro Dissolution Studies Y **2.7.1.4** **Appendix**	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature Y** **3.2.S.1.2** **Structure Y** **3.2.S.1.3** **General Properties Y**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers Y 2. Manufacturing Responsibilities Y 3. Type II DMF number for API (IBU – DMF # (b) (4) (Diphenhydra – DMF # (b) (4) 4. CFN or FEI numbers Y	☒
3.2.S.3	**Characterization**	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) Y **3.2.S.4.2** **Analytical Procedures** Y **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples Y 2. Samples-Statement of Availability and Identification of: a. Drug Substance Y b. Same lot number(s) Y **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) Y 2. Applicant certificate of analysis Y **3.2.S.4.5** **Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition YES 2) Inactive ingredients are appropriate per IIG (See Attached IIG Search Table)	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) Y 2. CGMP Certification: YES 3. Function or Responsibility Y **(See Amendment Dated December 4, 2007)** 4. CFN or FEI numbers (CFN1811666) **3.2.P.3.2** **Batch Formula** Batch Formulation Y **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Y 3. If sterile product: Aseptic fill / Terminal sterilization NA 4. Reprocessing Statement Y **3.2.P.3.4** **Controls of Critical Steps and Intermediates** **3.2.P.3.5** **Process Validation and/or Evaluation** 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified Y (Located in 3.2.R.1.P.2 – Info on Components) **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) Y 2. Suppliers' COA (specifications and test results) Y **3.2.P.4.2** **Analytical Procedures** **3.2.P.4.3** **Validation of Analytical Procedures** **3.2.P.4.4** **Justification of Specifications** Applicant COA Y	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** Y **3.2.P.5.2** **Analytical Procedures** Y **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Y 2. Same lot numbers Y **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form Y **3.2.P.5.5** **Characterization of Impurities** **3.2.P.5.6** **Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data Y 3. Packaging Configuration and Sizes Y 4. Container/Closure Testing Y 5. Source of supply and suppliers address (Located in 3.2.R.1.P.2 – Info on Components)	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted Y 2. Expiration Dating Period 24 months **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Y **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data Y 2. Batch numbers on stability records the same as the test batch **Y**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available)** **3.2.R.2.S** **Comparability Protocols** **3.2.R.3.S** **Methods Validation Package** Y Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation Y (See attached) Theoretical Yield Actual Yield Packaged Yield **3.2.R.1.P.2** **Information on Components** Y **3.2.R.2.P** **Comparability Protocols** **3.2.R.3.P** **Methods Validation Package** Y Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) NA b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) NA **2. Lot Numbers of Products used in BE Study(ies):** (SEE ATTACHED) **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
	5.3.1.2 **Comparative BA/BE Study Reports** 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Y 2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study Table 7. Incidence of Adverse Events in Individual Studies Table 8. Reanalysis of Study Samples **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies Y Table 5. Formulation Data Y **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation **5.3.7** **Case Report Forms and Individual Patient Listing**	☒

5.4	**Literature References**	
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES) (**i.e., fasting/fed/sprinkle) FASTING AND FED ON 200 MG/38 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Y 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES) (**i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐

TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES) NO

Study Type

1. Pilot Study (determination of ED50)
2. Pivotal Study (study meets BE criteria 90%CI of 80-125)

TRANSDERMAL DELIVERY SYSTEMS NO

Study Type

1. In-Vivo PK Study
    1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC)
    2. In-Vitro Dissolution
    3. EDR Email: Data Files Submitted
2. Adhesion Study
3. Skin Irritation/Sensitization Study

Updated 10/10/2006 C. Bina

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition of the Drug Product

What are the components and composition of the final product? What are the functions(s) of each excipient?

The drug product consists of 200 mg Ibuprofen (IBU) and 38 mg Diphenhydramine Citrate (DPC) as active substances per tablet. The quantitative composition and function of each component in the drug product is listed in the table below.

Ingredient	Function	Weight mg/tablet	% (w/w)
Diphenhydramine Citrate, USP	Active Ingredient	38.0	(b) (4)
Ibuprofen, USP	Active Ingredient	200.0	(b) (4)
Colloidal Silicon Dioxide, NF			(b) (4)
Croscarmellose Sodium, NF			
FD&C Blue #2			
Glyceryl Behenate, NF			
Hydroxypropylcellulose, NF			
Iron Oxide Black			
Lactose Monohydrate, NF			
Magnesium Stearate, NF			
Microcrystalline Cellulose, NF			
Polyethylene Glycol, USP			
Polyvinyl Alcohol, USP			
Pregelatinized Starch, NF			
(b) (4)			
Talc, USP			
Titanium Dioxide, USP			
Total Weight		(b)	**100.00**

(b) (4)

INACTIVE INGREDIENT SEARCH TABLE

Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg
ANDA 79-113, Perrigo R&D Co.

SILICON DIOXIDE, COLLOIDAL	(b) (4)
CROSCARMELLOSE SODIUM	
FD&C BLUE NO. 2*	
GLYCERYL BEHENATE	
HYDROXYPROPYL CELLULOSE	
(b) (4)	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
STARCH 1500, PREGELATINIZED	
TALC *	
TITANIUM DIOXIDE *	
POLYVINYL ALCOHOL *	
POLYETHYLENE GLYCOL 3350 *	

* (b) (4)

(b) (4)

QUANTITATIVE FORMULA

PRODUCT IDENTIFIER: (b) (4)

PRODUCT DESCRIPTION: (b) (4)

(b) (4)

****** CONFIDENTIAL ******

ISSUED TO : 1328 Perrigo Company

Current Date: 22-MAY-2007

(b) (4)

MODULE 2.7.6: Synopsis of Individual Studies

Type of Study	Study Identifier	Study Objective	Study Design; Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	R06-0740	This study compared the relative bioavailability (rate and extent of absorption) of 200 mg/38 mg Ibuprofen/Diphenhydramine Citrate Tablets by Perrigo R&D Company with that of ADVIL® PM Caplets by Wyeth Consumer Healthcare following a single oral dose (1 x 200 mg/38 mg caplet) in healthy adult volunteers administered under fasting conditions.	Crossover	1 Tablet, 200 mg/38 mg, oral	44 (44 completed)	Healthy adult subjects	Single dose	Complete
BE	R06-0741	This study compared the relative bioavailability (rate and extent of absorption) of 200 mg/38 mg Ibuprofen/Diphenhydramine Citrate Caplet by Perrigo R&D Company with that of ADVIL® PM Caplets by Wyeth Consumer Healthcare following a single oral dose (1 x 200 mg/38 mg tablet or caplet) in healthy adult volunteers administered under non-fasting conditions.	Crossover	1 Tablet, 200 mg/38 mg, oral	44 (44 completed)	Healthy adult subjects	Single dose	Complete

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Ibuprofen N=44				
Parameter	**Test**	**Reference**	**% Ratio**	**90% CI**
AUC_{0-t} (ng-hr/mL)	75110.36	77094.39	97.43	(95.43, 99.47)
AUC_{0-8} (ng-hr/mL)	75948.44	77950.40	97.43	(95.41, 99.5)
C_{max} (ng/mL)	20400.03	22385.61	91.13	(86.38, 96.14)

For the ln-transformed diphenhydramine data, the 90% confidence intervals about the ratio of the test geometric mean to the reference geometric mean were within the 80% to 125% limits for AUC_{0-t}, AUC_{0-8}, and C_{max} (set by FDA, Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, Center for Drug Evaluation and Research [CDER], March, 2003)

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Diphenhydramine N=44				
Parameter	**Test**	**Reference**	**% Ratio**	**90% CI**
AUC_{0-t} (ng-hr/mL)	318.03	318.21	99.94	(96.81, 103.18)
AUC_{0-8} (ng-hr/mL)	337.11	335.17	100.58	(97.54, 103.71)
C_{max} (ng/mL)	37.97	38.05	99.79	(95.54, 104.23)

CONCLUSIONS: The results of this study indicate bioequivalence between the test and reference products under fasting conditions.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Ibuprofen N=44				
Parameter	**Test**	**Reference**	**% Ratio**	**90% CI**
AUC_{0-t} (ng-hr/mL)	61181.42	63721.44	96.01	(93.49, 98.6)
$AUC_{0-\infty}$ (ng-hr/mL)	61958.52	64540.36	96.00	(93.47, 98.6)
C_{max} (ng/mL)	15446.87	16451.19	93.90	(87.6, 100.64)

For the ln-transformed diphenhydramine data, the 90% confidence intervals about the ratio of the test geometric mean to the reference geometric mean were within the 80% to 125% limits for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} (set by FDA, Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, Center for Drug Evaluation and Research [CDER], March, 2003).

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Diphenhydramine N=43				
Parameter	**Test**	**Reference**	**% Ratio**	**90% CI**
AUC_{0-t} (ng-hr/mL)	318.10	351.02	90.62	(85.42, 96.14)
$AUC_{0-\infty}$ (ng-hr/mL)	333.99	363.64	91.85	(86.63, 97.38)
C_{max} (ng/mL)	37.57	42.55	88.30	(84.03, 92.78)

CONCLUSIONS: The results of this study indicate bioequivalence between the test and reference products under non-fasting conditions.

No serious adverse events were reported over the course of the study.

Overall, ibuprofen/diphenhydramine citrate was well tolerated as a single oral dose (1 x 200 mg/ 38 mg tablet or caplet) administered under non-fasting conditions.

What is the reconciliation of the exhibit batch?

The reconciliation of the executed batch record for the exhibit batch at each stage is provided in the tables on the following pages. For exhibit batch records, refer to ***Module R.1.P***.

(b) (4)


(b) (4)


(b) (4)

Notification of New Correspondence

PERRIGO

Regulatory Affairs Department
Fax: 269-673-7655

FACSIMILE TRANSMISSION

DATE: ***December 4, 2007***

TO: ***Kwadwo Awuah***
Fax 301-443-3847

COMPANY: **FDA**
Office of Generic Drugs

FROM: ***David A. Kloosterman***
Project Manager, ANDA Regulatory Affairs

TEL. # ***269-673-1482***

NUMBER OF PAGES (INCLUDING COVER PAGE) 9

MESSAGE:

Per your request, attached you will find a fax copy of portions of a New Correspondence submission relative to ANDA 079113 (Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/ 38 mg). The following pages provide copies of the Cover Letter, Attachment, and the 356h form from the indicated New Correspondence submission. As noted in the attached letter, the original documents for this New Correspondence have been sent to FDA via express mail service.

Best regards,

David A. Kloosterman

Please call David Kloosterman at (269) 673-1482 if there are transmission problems.

PERRIGO®

December 3, 2007

New Correspondence

Gary Buehler, Director
Office of Generic Drugs (HFD-600)
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Via Facsimile and Federal Express

Re: ANDA #079113
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/ 38 mg
Over-The-Counter Drug Product
New Correspondence

Dear Mr. Buehler:

Reference is made to ANDA 079113 for Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/ 38 mg, submitted on August 17, 2007.

Perrigo R&D Company (Perrigo) hereby submits this New Correspondence to ANDA 079113 in response to comments from Kwadwo Awuah, Regulatory Reviewer, Regulatory Support Branch, received via telephone on November 20, 2007. Please note that this electronic application has been organized according to the ICH electronic Common Technical Document (eCTD) format. This communication is classified as NEW CORRESPONDENCE.

OGD Comment 1:

1. *Please submit more specific information regarding the function of the outside labs.*

Perrigo Response 1:

1. Information regarding the function of the outside labs is located in the original ANDA submission in Module 3, Section 3.2.P.3.1. To clarify, the following contract quality control laboratories may be used for testing of the drug substance, inactive ingredients, and/or drug product:

(b) (4)

[redacted]

515 Eastern Avenue
Allegan, Michigan 49010
(269) 673-8451

(b) (4)

The following contract quality control laboratories may be used for the testing of the packaging components:

(b) (4)

This information is now reflected in the amended sections of Module 3, Sections 3.2.P.3.1 (Manufacturers) and 3.2.R.1.P.2 (Information on Components). In addition, notes regarding testing done by these laboratories specifically to support this application have been added to Section 3.2.R.1.P.2 (see especially subsection 3.2.R.1.P.2.4).

OGD Comment 2:

2. *Please provide the quantitative formula for the Opadry II excipient.*

Perrigo Response 2:

2. The quantitative formula for the excipient (b) (4) is provided in our original ANDA application in the Tables in Sections 2.3.P.1, 2.3.P.3, 3.2.P.1.3, 3.2.P.2.1.2 and 3.2.P.3.2, in which the amounts of each component of the (b) excipient are provided in terms of mg/ tablet (or mg/ unit dose), kg/ (b) (4) tablets (Exhibit Batch size), kg (b) tablets (Commercial Batch size), and/or %w/w (with respect to the tablet formula). We note also that the amounts of these components per tablet are compared to the IIG levels in Sections 2.3.P.1 and 3.2.P.2.1.2.

For convenience, the quantitative formula for the excipient (b) (4) is shown below:

% W/W	Ingredient
(b) (4)	

In addition, we attach the Quantitative Formula provided to Perrigo by the manufacturer (b) (4) see Attachment 1). This document is included in the amended Subsection 3.2.P.2.1.2 of Section 3.2.P.2.1.

Included in this submission is a certification that a letter has been sent to the FDA's Detroit District Office informing them that an eCTD New Correspondence to ANDA #079113 for Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/ 38 mg, has been submitted to the FDA's Office of Generic Drugs (OGD), CDER, and that OGD will notify them when they can access the technical section of the application.

This submission includes one (1) CD-ROM disk of approximately 1 MB in size and is in a fully electronic CTD format. The disk containing our submission has been checked for viruses using McAfee® VirusScan® Enterprise 8.0.0.

If you have any questions or concerns, please contact me immediately at (269) 673-1482.

Respectfully submitted,

David A. Kloosterman
Regulatory Affairs Project Manager

Attachment 1

Quantitative Formula of (b) (4)

as provided by the manufacturer

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Perrigo R&D Company	DEC 3 2007
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(269)-673-8451	(269)-673-7655
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 515 Eastern Avenue Allegan, MI 49010	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(if previously issued)* 079113

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/ 38 mg	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Benzeneacetic acid, -methyl-4-(2-methylpropyl), (+/-)- and Ethanamine, 2-(diphenylmethoxy)-N,N-dimethyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1),	050

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	200mg (Ibuprofen)/ 38mg (Diphenhydramine Citrate)	Oral

(PROPOSED) INDICATION(S) FOR USE:

For relief of occasional sleeplesness when associated with minor aches and pains. Helps you fall asleep and stay asleep.

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*
☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Advil®PM Caplets Holder of Approved Application Wyeth Consumer Healthcare

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
New Correspondence in rewponse to request for information.

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Drug Substance manufacturing, packaging and control: See Section 3.2.S.1
Drug Product manufacturing, packaging and control: See Section 3.2.P.3.1.1

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMFs	[redacted] (b) (4)

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature]	Valerie Gallagher, Associate Director NDA/ ANDA Regulatory Affairs	DEC 3 2007
ADDRESS *(Street, City, State, and ZIP Code)* 515 Eastern Ave., Allegan, MI 49010		Telephone Number (269) 673-8451

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : September 18, 2007

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 79-113 for Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg to determine if the application is substantially complete for filing.

Perrigo R & D Company has submitted ANDA 79-113 for Ibuprofen and Diphenhydramine Citrate Tablets, 200 mg/38 mg. It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Perrigo R & D Comapny on August 17, 2007 for its Ibuprofen and Diphenhydramine Citrate product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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/s/

Eda Howard
9/19/2007 08:25:35 AM
APPLICATIONS EXA