CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-429

CHEMISTRY REVIEW(S)

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Nonprescription Clinical Evaluation
NDA:	22-429
Applicant:.	Banner Pharmacaps Inc.
Stamp Date:	Aug. 1, 2008
PDUFA Date	June 1, 2009
Trademark:	Not provided
Established Name:	Cetirizine hydrochloride
Dosage Form:	Immediate Release Soft Gelatin Capsule
Route of Administration:	Oral
Indication:	Temporary relief of symptoms of hay fever or other upper respiratory allergies, and relief of itching due to hives
PAL:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues

A. Summary

This NDA is submitted by Banner Pharmacap under section 505(b) (2) of the Federal Food Drug and Cosmetic Act in support of the nonprescription marketing of cetirizine HCl soft gelatin capsules 5 mg and 10 mg for the treatment of seasonal allergy and hives. The listed drug is Zyrtec tablets 10 mg (NDA 19-835). Banner conducted two bioequivalence studies in fed and fast states for the 10 mg capsules to support the NDA.

The drug substance, cetirizine hydrochloride, is referenced to DMF ——held by—— DMF—— has been reviewed multiple times and deemed adequate to support referenced submissions which include —— b(4)

The proposed drug product is an ——immediate-release, liquid filled soft gelatin capsule —— The to-be-marketed formulation is the same formulation used in the pivotal bioequivalence studies and registration stability batches. In addition to the active pharmaceutical ingredient, the proposed product is formulated using the following excipients and manufacturing aids: polyethylene glycol 400, NF; sodium hydroxide, NF; purified water, USP; gelatin, NF; glycerin, USP; sorbitol sorbitan solution, NF —— b(4)
——; FD&C Yellow #6; FD&C Red#40, FD&C Blue #1, ——

The proposed product packaging is [redacted] bottles with a [redacted] tamper-evident [redacted] Two capsule counts are proposed: 20 and 200. The size of the bottle varies depends on strength and count.

The proposed commercial manufacturing scale is [redacted] capsules and [redacted] capsules per batch for 5 mg and 10 mg, respectively. The designated commercial site, Banner Pharmacaps in Highpoint, North Carolina, is also the manufacturing site of pivotal clinical supplies and registration stability batches. The manufacturing process consists of the following steps: [redacted] nformation regarding critical steps and in-process controls are provided in the NDA.

Stability data provided in the initial submission to support an expiry period of 24 months at controlled room temperature of 68-77°F (20-25°C) include long term (25°C/60% RH) data of 6-12 months, intermediate temperature (30°C/65% RH) data of 6-12 months, and accelerated temperature (40°C/75% RH) data of 6 months from 2 pilot-scale and one small-scale batches for each strength and for each of 20 and 200 counts. As to bulk packaging, 12 months of long term (25°C/60% RH) data from three batches are provided for each strength.

B. Critical issues for review

[redacted] DMF b(4)

- Letter of Authorization is not provided for DMF [redacted]. What is provided is a letter for notification of US agent.

Drug Product Manufacture

- The applicant states in the NDA that [redacted] b(4)

Drug Product Degradant Method Validation

- Method validation was based on surrogation using the parent compound. Peak purity check was performed but on the parent peak rather than on the degradant peak of interest.

Drug Product Specification

- Only one ID test is proposed.

Drug Product Container/Closure Systems

- The applicant does not clearly describe commercial configuration. The 20 and 200 counts on which the registration stability data have been generated appear to be for stability purpose only. CMC review can not be properly performed without an accurate understanding of the configurations sought for approval.

Lable/lableing

- Mock-up with proposed trade dressing is not provided for container labels.
- Trade name is not proposed by the applicant.

Biowaiver

- The applicant requests a biowaiver for the 5 mg capsules. An in-vitro dissolution comparison with an f_2 analysis was conducted by the applicant to support the biowaiver. However, the dissolution profile comparison was done only in one medium (pH 6.8 phosphate buffer). Usually, three media (pH 1, 4.5, and 6.8) are required. Per the e-mail dated Sep. 10, 2008 from ONDQA Biopharm Expert, Patrick Marroum, the applicant needs to submit data in the three media (pH 1, 4.5, and 6.8) before they can get the waiver.

C. Comments for 74-Day Letter

The following comments are to be conveyed to the applicant in the 74-day letter:

1. Clarify what are the intended to-be-marketed packaging configurations, especially about capsule counts and packaging components.
2. Provide mock-up of container labels with proposed trade dressing.
3. Provide a letter of authorization for DMF ——— b(4)
4. Provide comparative in-vitro dissolution data with f_2 analysis in media of pH 1 and pH 4.5 for 5 mg and 10 mg ——— capsules.

b(4)

D. Comments/Recommendation

This NDA is **fileable** from chemistry, manufacturing and controls (CMC) perspective. The major review issues include container/closure system, method validation, and biowaiver.

GMP inspections have been requested. The drug substance manufacturing site is in India. The drug product manufacturing site is in U.S.

Shulin Ding
Pharmaceutical Assessment Lead, Branch III

Moo-Jhong Rhee
Chief, Branch III

Filing Checklists

A. Administrative Checklists

YES	NO		Comments
x		On its face, is the section organized adequately?	
x		Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
x		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
x		Has an environmental assessment report or categorical exclusion been provided?	

B. Technical Checklists

1. Drug Substance: Cetirizine HCl referenced to DMF [redacted] b(4)

	x	Does the section contain synthetic scheme with in-process parameters?	Reference to DMF [redacted] b(4)
	x	Does the section contain structural elucidation data?	Reference to DMF [redacted] b(4)
x		Does the section contain specifications?	
	x	Does the section contain information on impurities?	Reference to DMF [redacted] b(4)
x		Does the section contain validation data for analytical methods?	
	x	Does the section contain container and closure information?	Reference to DMF [redacted] b(4)
	x	Does the section contain stability data?	Reference to DMF [redacted] b(4)

2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	Missing bottling operation
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	Unclear in to-be-marketed tablet counts.
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	Missing trade dressing.
x		Does the section contain tradename and established name?	Trade name not proposed.

C. Review Issues

x		Has all information requested during the IND phases, and at the	

		pre-NDA meetings been included?	
	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	LOA not provided for DMF [redacted] 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/

Shulin Ding
9/25/2008 04:19:02 PM
CHEMIST

Moo-Jhong Rhee
9/25/2008 06:06:21 PM
CHEMIST
Chief, Branch III

NDA 22-429

Certirizine

Banner Pharmacaps, Inc.

Christopher Hough

Review Chemist

Office of New Drug Quality Assessment
Division of Office of New Drug Quality Assessment
Pre-Marketing Division II, Branch III

CMC REVIEW OF NDA 22 429

Non-Prescription Drug Products
(HFD-560)

Table of Contents

CMC Review Data Sheet

1. NDA 22-429

2. REVIEW #: 1

3. REVIEW DATE: 10-Apr-2009

4. REVIEWER: Christopher Hough, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	31 July 2008
Correspondence (C)	
Amendment (BC)	08-Sep-2008
Amendment (BC)	25-Sep-2008
Amendment (BC)	29-Oct-2008
Amendment (BC)	08-Dec-2008
Amendment (BC)	10-Feb-2009
Amendment (BC)	13-Feb-2009
Amendment (BC)	13-Mar-2009
Amendment (BC)	24-Mar-2009
Amendment (BC)	3-Apr-2009
Amendment (BC)	14-Apr-2009
Amendment (BC)	21-Apr-2009
Amendment (BC)	12-May-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Banner Pharmacaps, Inc.
Address:	4125 Premier Drive, High Point, NC 27265
Representative:	Dana Toops, Director, Regulatory Affairs
Telephone:	(336) 812-8700 ext. 23312

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name: certirizine HCl
c) Code Name/# (ONDQA only): N/A

CMC Review Data Sheet

d) Chem. Type/Submission Priority (ONDQA only): new dosage form, Rx to OTC switch
- Chem. Type: Antihistamine
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2)

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx _✓_OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

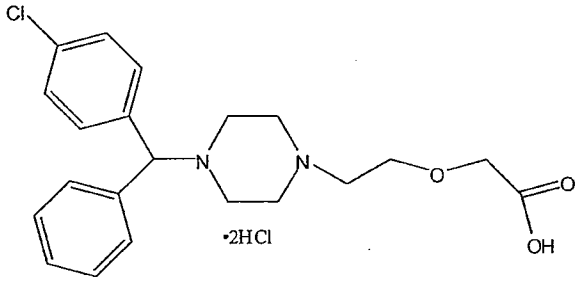
___SPOTS product – Form Completed

___✓___Not a SPOTS product

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

(*RS*)-2-[2-[4-[(4-Chlorophenyl)phenylmethyl] Piperazin-1-yl]ethoxy]acetic acid dihydrochloride

Certirizine HCl,



$C_{12}H_{27}Cl_3N_2O_3$

461.8

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
14194	IV	Banner	[redacted] or capsules	3	Adequate	02-Aug-2007	Craig Bertha
[redacted]					Adequate	14-Apr-2008	Mike Darj
					Adequate	23-May-2007	Donna Christner
					Adequate	05-Nov-2004	Donald Klein
					Adequate	23-Jun-2006	Josephine Jee
					Adequate	23-Jun-2006	Josephine Jee
					Adequate	16-Nov-2007	Craig Bertha
					See Note	22-Sep-2004	Swapan De
					Adequate	24-Sep-2007	Craig Bertha
					Adequate	27-Jul-2004	Sarah Pope
					Adequate	07-Dec-2004	Rapti Madurawe
					Adequate	08-Dec-2006	Gene Holbert
					Adequate	3-Apr-2009	Chris Hough
					Adequate	22-Dec-2008	Craig Berthaq

b(4)

b(4)

b(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")
Note: Included for [redacted]

b(4)

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
Comments: DMF [redacted] has never been reviewed since the original master file of 10-Jul-2003. Its composition has not changed since the [redacted] *The master file is deemed adequate.*

b(4)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	N/A	N/A

CMC Review Data Sheet

NDA	RLD, NDA 19-835	Zyrtec® Tablets 10 mg & 5 mg

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biopharmaceutics	Bio-waiver recommended	19-Jan-2009	Tapash Ghosh
EES	Acceptable	6-Dec-2008	Office of Compliance
Pharm/Tox			
Biopharm	Bioequivalent to RLD	09-Sep-2008	Yun Xu
LNC			
Methods Validation	N/A, according to the current ONDQA policy	-	-
DMETS	Currently under review		
EA	Categorical exclusion requested and found acceptable	29-Apr-2009	Christopher Hough
Microbiology	N/A		

The CMC Review for NDA 22-429

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. Therefore, from the CMC perspective, this NDA is recommended for approval.

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

None.

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance, cetirizine dihydrochloride (cetirizine HCl), is manufactured by [redacted] The specification of the drug substance is based on the European Pharmacopoeia monograph and deemed acceptable (at present time, only a draft USP monograph is available). The sponsor cross references to DMF# [redacted] for the [redacted] b(4)
Cetirizine HCl is used in a number of approved drugs in the U.S., both prescription and OTC. The Reference Listed Drug for this application is Zyrtec® Tablets, 10 mg, currently approved for McNeil Consumer Healthcare. The sponsor added at the request of Agency the tests for residual solvents including [redacted] b(4)
The manufacturer uses a non-specific, non-stability indicating potentiometric pH titration assay method for the drug substance. However, since the sponsor uses an HPLC method for assaying cetirizine HCl in the drug product, the titration method for the drug substance is deemed acceptable. The stability of the drug substance appears to be remarkably resistant to heat, acid, base, oxidation and light. The acceptance criterion for assay for release of the drug substance is a tight 99.0 – 100.5%. Based on the available stability data, a retest period of [redacted] is granted. b(4)

(2) Drug Product

The drug product is a soft gelatin capsule containing 5 or 10 mg of cetirizine HCl in a [redacted] liquid fill. The excipients include polyethylene glycol, sodium hydroxide, and b(4)

[redacted] and [redacted] gelatin, glycerin, sorbitol, water, and [redacted] b(4)
for the [redacted] All clinical studies were conducted with a [redacted]
formulation that contained [redacted] but the sponsor notified FDA in an
April 23, 2009 amendment that for [redacted] b(4)
[redacted], which were present in minute
quantities' should have no effect on the performance of the drug product and is
considered acceptable. All the ingredients are USP/NF grades, except for cetirizine
HCl [redacted]
[redacted] b(4)
[redacted]
[redacted] There has been some
concern raised on the [redacted] b(4)
[redacted]
[redacted]
[redacted] hese degradation products would not pose any safety issues because their
[redacted] The only known impurity detected at sufficient levels to report was b(4)
the "Impurity A",
[redacted] cetirizine HCl was detected in 6 month stability studies under the
accelerated conditions, [redacted]
[redacted]
Based on available stability data, an expiration dating period of 24 months is granted.

[redacted] b(4)
[redacted]

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

The drug product is to be taken orally, as a soft gelatin capsule, once daily. The over-the-counter dose is 10 mg, but 5 mg is also available for children.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided adequate information on raw material controls, manufacturing processes, process controls, specifications and analytical methods to assure consistent drug substance and drug product quality. The NDA also has provided sufficient drug product stability data to assure its strength, purity and quality for the duration of its proposed 24-month expiration dating period.

All facilities have acceptable site recommendations.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Christopher J. Hough, Ph.D.

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch III, ONDQA

C. CC Block: entered electronically in DFS

32 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Christopher Hough
5/14/2009 03:23:46 PM
CHEMIST

Marie Kowblansky
5/14/2009 04:10:47 PM
CHEMIST
Acting Branch Chief for Moo-Jhong Rhee

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22429/000	**Action Goal:**	
Stamp Date:	01-AUG-2008	**District Goal:**	02-APR-2009
Regulatory:	01-SEP-2009		
		Brand Name:	CETIRIZINE HCL CAPSULES
Applicant:	BANNER PHARMACAPS	**Estab. Name:**	
	4125 PREMIER DR	**Generic Name:**	CETIRIZINE HCL CAPSULES
	HIGH POINT, NC 27265	**Dosage Form:**	(CAPSULE)
Priority:	3	**Strength:**	5 MG AND 10 MG
Org. Code:	560		

Application Comment:

FDA Contacts:	S. GOLDIE	Project Manager	301-796-2055
	C. HOUGH	Review Chemist	301-796-0323
	S. DING	Team Leader	301-796-1349

Overall Recommendation:	ACCEPTABLE	on 06-NOV-2008	by S. ADAMS	()	301-827-2443

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 1063522 **FEI:** 3001451366

BANNER PHARMACAPS INC

4125 PREMIER DR
HIGH POINT, NC 272658144

DMF No: 14194 **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Estab. Comment:

Profile: CAPSULES, SOFT GELATIN **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	25-SEP-2008				DINGS
SUBMITTED TO DO	29-SEP-2008	10-Day Letter			FERGUSONS
DO RECOMMENDATION	30-SEP-2008			ACCEPTABLE	MWOLESKE
A GMP INSPECTION WAS CONDUCTED 10/11-15/2007 AND CLASSIFIED AS VOLUNTARY ACTION INDICATED (VAI). PROFILE CSG WAS JUDGED ACCEPTABLE. THE DISTRICT'S RECOMMENDATION IS ACCEPTABLE.				BASED ON FILE REVIEW	
OC RECOMMENDATION	30-SEP-2008			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** [redacted] **FEI:** [redacted]

[redacted] b(4)

DMF No: [redacted] **AADA:**

Responsibilities: [redacted]

Estab. Comment:

Profile: [redacted] b(4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	25-SEP-2008				DINGS
SUBMITTED TO DO	07-OCT-2008	GMP Inspection			ADAMSS
DO RECOMMENDATION	04-NOV-2008			ACCEPTABLE	ADAMSS
				BASED ON FILE REVIEW	
OC RECOMMENDATION	06-NOV-2008			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** [redacted] **FEI:** [redacted]

b(4)

DMF No: **AADA:**

Responsibilities: [redacted] b(4)

Estab. Comment:

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	25-SEP-2008				DINGS
OC RECOMMENDATION	29-SEP-2008			ACCEPTABLE BASED ON PROFILE	FERGUSONS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** [redacted] **FEI:** b(4)

[redacted]

DMF No: **AADA:** b(4)

Responsibilities: [redacted]

Estab. Comment:

Profile: CAPSULES [redacted] b(4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	26-SEP-2008				DINGS
OC RECOMMENDATION	29-SEP-2008			ACCEPTABLE BASED ON PROFILE	FERGUSONS