

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-392

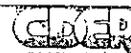
Chemistry Review(s)

NDA 21-392

**Cardizem LA
Extended-Release Tablets**

Biovail Laboratories Incorporated

**Ramsharan D. Mittal
Division of Cardio-Renal Drug Products**

**Chemistry Review Data Sheet**

1. NDA 21-392
2. REVIEW #: 4
3. REVIEW DATE: 6-JANUARY-2003
4. REVIEWER: Ramsharan D. Mittal

5. PREVIOUS DOCUMENTS: :

Submission(s) Reviewed	Document Date
N000	08-JUN-2001
N000-AZ	22-AUG-2001
N-BC	17-OCT-2001
N000-AC	11-JAN-2002
N000-BC	01-MAY-2002
N000-BC	31-MAY-2002

6. SUBMISSION(S) BEING REVIEWED :

Submission(s) Reviewed	Document Date
N000-BC	16-JUL-2002
N000-BZ	17-JUL-2002
N000-BC	21-AUG-2002
N000-BC	02-DEC-2002
N000-BC	18-DEC-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Biovail Laboratories Incorporated

Address: Chelston Park Building 2
Collymore Rock, St. Michael BHI, Barbados WI

Representative: John B. Dubeck (U.S. Agent)

Telephone: 202-434-4125

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cardizem LA
- b) Non-Proprietary Name (USAN): Diltiazem Hydrochloride Extended Release Tablets
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
Chem. Type: 3 Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL. CATEGORY: Calcium Channel Blocker
11. DOSAGE FORM: Extended Release Tablets
12. STRENGTH/POTENCY: 120, 180, 240, 300, 360, and 420 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:

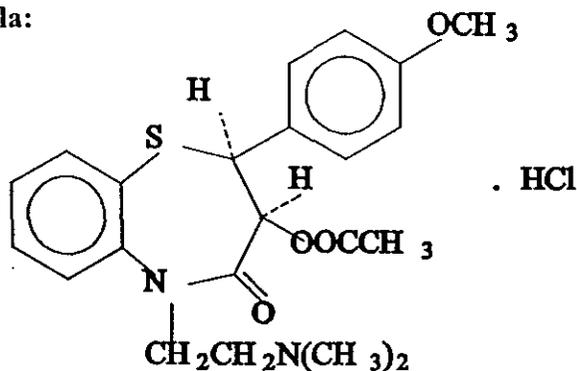
Chemical Name:

cis-(+)-3-Acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride.

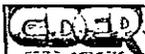
Molecular Formula: $C_{22}H_{26}N_2O_4S \cdot HCl$

Molecular Weight: 450.99

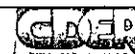
Structural Formula:



Diltiazem Hydrochloride



CHEMISTRY REVIEW



Chemistry Review Data Sheet

A. DMFs: Raw Materials

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II		Diltiazem Hydrochloride	3	Adequate Withdrawn	Nov, 30, 1999 L. Tang Amendment 12-18-02	Active. The status of this facility was adequate but facility has been withdrawn on 12-18-02
	II		Diltiazem Hydrochloride	3	Adequate	Feb. 14, 2000 S. Basaran	Active
	II			4	N/A		
	II			4	N/A		
	II			4	N/A		
	II			4	N/A		
	II			3	Adequate	March 1, 2001 Dr. J. Salemme	
	II			4	N/A		
	II			4	N/A		
	II			4	N/A		
	II			4	N/A		

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

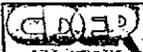
4 - Sufficient information in application

5 - Authority to reference not granted

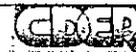
6 - DMF not available

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)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. DMFs: Packaging Material

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	Sep. 15, 2000	Packaging Component
	II			3	Adequate	Sep. 22, 2000	/
	II			3	Adequate	March 22, 2001	Packaging Component
	II			3	Adequate	Dec. 05, 1999 Nov. 23, 1994	Closure
	II			3	Adequate	Sep. 22, 1997	Closure
	II			3	Adequate	April 01, 1993	Packaging Component
	II			3	Adequate	Aug. 20, 2001	Packaging Component
	II			3	Adequate	March 13, 1996	
	II			3	Adequate	Feb. 3, 2002	/
	II			3	Sufficient	March 06, 1995	Packaging Component
	II			3	Adequate	Oct. 30, 1997	Packaging Component

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)

17. RELATED/SUPPORTING DOCUMENTS:

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,787	Cardizem - (Diltiazem HCl) IND for 180 and 240 mg tablets - Biovail
NDA	20-939	Diltiazem HCl, Extended Release Capsules, 120, 180, 240 and 300 mg, Biovail



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS::

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A (No statistical analysis of the stability data)		
EES	Acceptable	5-22-02	S. Adams (HFD-324)
Pharm/Tox	N/A		
Biopharm	Specifications Modified Acceptable	5-31-02 1-02-03	Gabriel J. Robbie Lydia Velazquez
LNC	N/A		
Methods Validation	To be submitted		
DMETS	Trade Name Not Acceptable "Once-a-Day-Dosage" statement is acceptable Trade Name Cardizem LA is Acceptable	5-31-02 7-10-02 11-8-02	Jennifer Fan Jennifer Fan Jennifer Fan
EA	Acceptable		
Microbiology	N/A		

Appears This Way
On Original

The Chemistry Review for NDA 21-392

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Deficiencies related to equivalency of the drug substance supplied by [redacted] supplied drug substance were not addressed satisfactorily. Applicant introduced new blister packaging [redacted] and did not provide description and DMF related information for this container/closure system. The applicant has now withdrawn (amendment dated 12-0202) references to [redacted] and has also withdrawn [redacted] blister packaging. As a result of these withdrawals all pending deficiencies have been resolved and from CMC perspective, the application may be approved.

Cardizem LA 120, 180, 240, 300, 360, and 420 mg tablets are packaged in configurations of 30, 90, and 1000 counts in [redacted] Bottles, and 7 tablets in blisters made of [redacted] with a [redacted] aluminum foil backing. The 30 and 90 count configurations with Child Resistant Closure (CRC) are intended for patient distribution and 1000 count bottles with non-CRC are intended for hospitals and pharmaceutical distribution only. Each bottle contains a [redacted]. The action letter should state that based on the stability data provided, the expiration date for Cardizem LA packaged in [redacted] bottles and [redacted] blisters will be 18 months.

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 and Drug Substance

- Diltiazem Hydrochloride Extended Release Tablets are intended for once-daily administration. Pharmacokinetic data from two studies demonstrated that Diltiazem Hydrochloride Extended Release Tablets are bioequivalent to Diltiazem Hydrochloride Extended Release Capsules approved in the applicant's NDA 20-939. The mechanism of the extended release tablets involves beads containing the active and inactive ingredients, [redacted]

[redacted] The beads are combined with other excipients and compressed into tablets.

- Diltiazem Hydrochloride USP is a well-known active ingredient and is listed in USP. Diltiazem Hydrochloride drug substance has two chiral centers and is

manufactured by [redacted] Diltiazem Hydrochloride is freely soluble in Chloroform, Methanol, and Water and slightly soluble in Ethanol. For details on the structure, manufacture, and sources of Diltiazem Hydrochloride drug substance, the applicant provided references to two DMF #'s [redacted]. These DMFs have been reviewed and found to be satisfactory. Based on the drug substance stability data a [redacted] retest date for drug substance has been assigned. The applicant has now withdrawn references to [redacted] DMF # [redacted].

- The applicant submitted another NDA [redacted] (Cardizem [redacted], dated August 23, 2001, which was converted to a major amendment to pending NDA 21-392 (this NDA.). The reason is that the drug formulation in both NDAs is the same and the difference between the two applications is in the time of administration of the drug (am versus pm). The Clinical Division therefore decided that [redacted] should be nothing more than an amendment to 21-392 and the applicant agreed to this.
- The application was amended (11 Jan., 2002) to include additional strengths of 120 mg, 180 mg, and 420 mg Extended Release Tablets. The previously approved Diltiazem HCl Extended Release Capsules NDA 20-939 has 120 mg and 180 mg strengths but does not have any strength equivalent to 420 mg tablets.
- Based on 18 months updated stability data for 240 mg, 300 mg, and 360 mg and 9 months stability data for 120 mg, 180 mg, and 420 mg tablets and [redacted] accelerated data for all strengths an expiration date of 18 months for all strengths packaged in [redacted] bottles and [redacted] with a [redacted] aluminum foil backing blisters can be assigned.
- The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed this NDA. They suggested more dissolution time points and specifications for evaluating additional dissolution data. However, considering that all the stability data were generated by the sponsor using their proposed specifications, OCPB has suggested that the firm's dissolution time points can be used on an interim basis (one year) for evaluation of the stability data and assignment of an expiration date. The final product specifications will be updated on the basis of OCPB recommendations.
- DMETS has recommend the approval of the modifier "LA" in conjunction with the proprietary name and has no objection to the Trade Name Cardizem LA.
- Overall recommendation from Office Of Compliance is "Acceptable" for the cGMP status of all facilities. The EER was attached to review # 3. As of the date of this review, there is no change to the status of any of the facility in the EES.

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

The product is proposed to be used for the treatment of hypertension, it may be used alone or in combination with other antihypertensive medications. Its pharmacology, pharmacokinetics, therapeutic efficacy and safety profile is well known. The Diltiazem Hydrochloride Extended Release Tablets 120 mg, 180 mg, 240 mg, 300 mg, 360 mg, and 420 mg are intended for once-daily administration. According to applicant, Clinical trials have studied doses 120 mg to 540 mg administered once daily at bedtime and in the morning. [

] The scoreline from earlier strengths has been removed and none of the tablet is scored.

Based on 18 months stability data for 240 mg, 300 mg, and 360 mg and [] stability data for 120 mg, 180 mg, and 420 mg tablets at 25°C/60%RH and [] accelerated data for all strengths at 40°C/75%RH, an expiration date of 18 months for all strengths packaged in — bottles and [] with a [] aluminum foil backing blisters is recommended.

C. Basis for Approvability or Not-Approval Recommendation

N/A.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

12 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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

/s/

Ramsharan Mittal
1/9/03 02:37:50 PM
CHEMIST

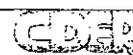
John Simmons ..
1/9/03 04:18:11 PM
CHEMIST
for K Srinivasachar

NDA 21-392

**Diltiazem Hydrochloride
Extended-Release Tablets**

Biovail Laboratories Incorporated

**Ramsharan D. Mittal
Division of Cardio-Renal Drug Products**



Chemistry Review Data Sheet

1. NDA 21-392
2. REVIEW #: 3
3. REVIEW DATE: 06-JUNE-2002
4. REVIEWER: Ramsharan D. Mittal
5. PREVIOUS DOCUMENTS: :

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
N000	08-JUN-2001
N000-AZ	22-AUG-2001
N-BC	17-OCT-2001
N000-AC	11-JAN-2002
N000-BC	01-MAY-2002

6. SUBMISSION(S) BEING REVIEWED :

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
N000-BC	31-MAY-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Biovail Laboratories Incorporated
Address: Chelston Park Building 2
Collymore Rock, St. Michael BHI, Barbados WI
Representative: John B. Dubeck (U.S. Agent)
Telephone: 202-434-4125

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cardizem —
b) Non-Proprietary Name (USAN): Diltiazem Hydrochloride Extended Release Tablets
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL. CATEGORY: Calcium Channel Blocker
11. DOSAGE FORM: Extended Release Tablets
12. STRENGTH/POTENCY: 120, 180, 240, 300, 360, and 420 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:

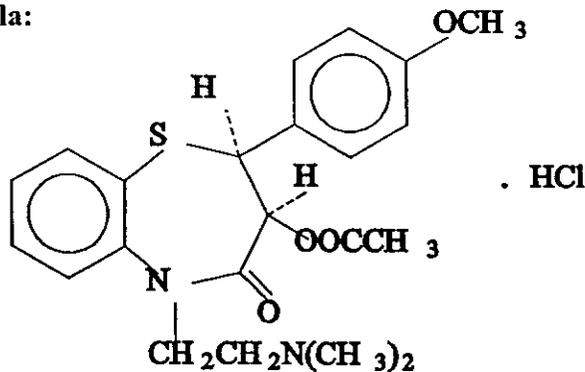
Chemical Name:

cis-(+)-3-Acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride.

Molecular Formula: $C_{22}H_{26}N_2O_4S \cdot HCl$

Molecular Weight: 450.99

Structural Formula:



Diltiazem Hydrochloride



CHEMISTRY REVIEW



Chemistry Review Data Sheet

A. DMFs: Raw Materials

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II		Diltiazem Hydrochloride	3	Adequate	Nov, 30, 1999 L. Tang	Active
	II		Diltiazem Hydrochloride	3	Adequate	Feb. 14, 2000 S. Basaran	Active
	II			4	N/A		
	II			4	N/A		
	II			4	N/A		
	II			4	N/A		
	II			3	Adequate	March 1, 2001 Dr. J. Salemm	
	II			4	N/A		
	II			4	N/A		
	II			4	N/A		
	II			4	N/A		

Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type I DMF

3 - Reviewed previously and no revision since last review

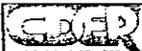
4 - Sufficient information in application

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)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. DMFs: Packaging Material

DMF =	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	Sep. 15, 2000	Packaging Component
	II			3	Adequate	Sep. 22, 2000	—
	II			3	Adequate	March 22, 2001	Packaging Component
	II			3	Adequate	Dec. 05, 1999 Nov. 23, 1994	Closure
	II			3	Adequate	Sep. 22, 1997	Closure
	II			3	Adequate	April 01, 1993	Packaging Component
	II			3	Adequate	Aug. 20, 2001	Packaging Component
	II			3	Adequate	March 13, 1996	—
	II			3	Adequate	Feb. 3, 2002	—
	II			3	Sufficient	March 06, 1995	Packaging Component
	II			3	Adequate	Oct. 30, 1997	Packaging Component

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

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5 – Authority to reference not granted

6 – DMF not available

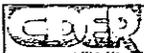
7 – Other (explain under "Comments")

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

17. RELATED/SUPPORTING DOCUMENTS:

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,787	Cardizem — (Diltiazem HCl) IND for 180 and 240 mg tablets - Biovail
NDA	20-939	Diltiazem HCl, Extended Release Capsules, 120, 180, 240 and 300 mg, Biovail



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS::

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A (No statistical analysis of the stability data)		
EES	Acceptable	5-22-02	S. Adams (HFD-324)
Pharm/Tox	N/A		
Biopharm	Specifications Modified	5-31-02	Gabriel J. Robbie
LNC	N/A		
Methods Validation	To be submitted		
DMETS	Trade Name Not Acceptable	5-31-02	Jennifer Fan
EA	Acceptable		
Microbiology	N/A		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.

Yes No If no, explain reason(s) below:

The Chemistry Review for NDA 21-392

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Some of the deficiencies noted in reviews 1 and 2 have still not been addressed satisfactorily and need to be resolved. These deficiencies are listed in the review. . The application is approvable pending a satisfactory resolution of the drug substance and drug product deficiencies noted in the Draft Deficiency section at the end of this review.

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 and Drug Substance

- Diltiazem Hydrochloride USP is a well-known active ingredient and is listed in USP. Diltiazem Hydrochloride drug substance has two chiral centers and is manufactured by [redacted] Diltiazem Hydrochloride is freely soluble in Chloroform, Methanol, and Water and slightly soluble in Ethanol. For details on the structure, manufacture, and sources of Diltiazem Hydrochloride drug substance, the applicant provided references to two DMF #'s [redacted] These DMFs have been reviewed and found to be satisfactory. Based on the drug substance stability data a [redacted] retest date for drug substance has been assigned.
- Diltiazem Hydrochloride Extended Release Tablets are intended for once-daily administration. Pharmacokinetic data from two studies demonstrated that Diltiazem Hydrochloride Extended Release Tablets are bioequivalent to Diltiazem Hydrochloride Extended Release Capsules approved in the applicant's NDA 20-939. The mechanism of the extended release tablets involves beads containing the active and inactive ingredients [redacted] The beads are combined with other excipients and compressed into tablets.
- The applicant submitted another NDA [redacted] (Cardizem [redacted], dated August 23, 2001 which was converted to a major amendment to pending NDA 21-392 (this NDA.). The reason is that the drug formulation in both NDAs is the same and the difference between the two applications is [redacted]

The Clinical Division therefore decided that [redacted] should be nothing more than an amendment to [redacted] and the applicant agreed to this.

- The application has been amended (11 Jan., 2002) to include additional strengths of 120 mg, 180 mg, and 420 mg Extended Release Tablets. The previously approved Diltiazem HCl Extended Release Capsules NDA 20-939 has 120 mg and 180 mg strengths but does not have any strength equivalent to 420 mg tablets.
- Based on [redacted]: updated data for 240 mg, 300 mg, and 360 mg and a very limited data for 120 mg, 180 mg, and 420 mg tablets an expiration date of [redacted] for all strengths can be assigned. The applicant's proposed expiry date of 18 months is not acceptable.
- The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed this NDA. They have proposed new dissolution times and specifications. However, considering that all the stability data were generated by the sponsor using their proposed specifications, OCPB has suggested that the firm's dissolution time points can be used on an interim basis for evaluation of the stability data and assignment of an expiration date.
- DMETS does not recommend the use of the modifier [redacted] in conjunction with the proprietary name. The applicant has suggested other proprietary names but these were received very late in the review cycle for consideration by DMETS to include in the action letter. At this stage the drug product does not have a proprietary name and the generic name "Diltiazem Hydrochloride Extended Release Tablet" will be used.
- Overall recommendation from Office Of Compliance is "Acceptable" for the cGMP status of all facilities. The EER is attached to this review.

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

The product is proposed to be used for the treatment of hypertension, it may be used alone or in combination with other antihypertensive medications. Its pharmacology, pharmacokinetics, therapeutic efficacy and safety profile is well known. The Diltiazem Hydrochloride Extended Release Tablets 120 mg, 180 mg, 240 mg, 300 mg, 360 mg, and 420 mg are intended for once-daily administration. According to applicant, Clinical trials have studied doses 120 mg to 540 mg administered once-daily at bedtime and in the morning. [redacted]

[redacted] The scoreline from earlier strengths has been removed and none of the tablet are scored.

C. Basis for Approvability or Not-Approval Recommendation

A list of the deficiencies pertaining to both drug substance and drug product that should be addressed is attached at the end of this review. The application is APPROVABLE from Chemistry Manufacturing and Controls standpoint pending a satisfactory resolution of these deficiencies.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

19 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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

/s/

Ramsharan Mittal
6/6/02 09:11:14 PM
CHEMIST

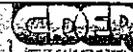
Kasturi Srinivasachar
6/6/02 09:17:52 PM
CHEMIST

NDA 21-392

**Diltiazem Hydrochloride
Extended-Release Tablets**

Biovail Laboratories Incorporated

**Ramsharan D. Mittal
Division of Cardio-Renal Drug Products**



Chemistry Review Data Sheet

1. NDA 21-392
2. REVIEW #: 2
3. REVIEW DATE: 22-MAY-2002
4. REVIEWER: Ramsharan D. Mittal
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
N000	08-JUN-2001
N000-AZ	22-AUG-2001
N000-BC	17-OCT-2001

6. SUBMISSION(S) BEING REVIEWED :

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
N000-AC	11-JAN-2002
N000-BC	01-MAY-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Biovail Laboratories Incorporated

Address: Chelston Park Building 2
Collymore Rock, St. Michael BHI, Barbados WI

Representative: John B. Dubeck (U.S. Agent)

Telephone: 202-434-4125

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cardizem —
- b) Non-Proprietary Name (USAN): Diltiazem Hydrochloride Extended Release Tablets
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL. CATEGORY: Calcium Channel Blocker
11. DOSAGE FORM: Extended Release Tablets
12. STRENGTH/POTENCY: 120, 180, 240, 300, 360, and 420 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:

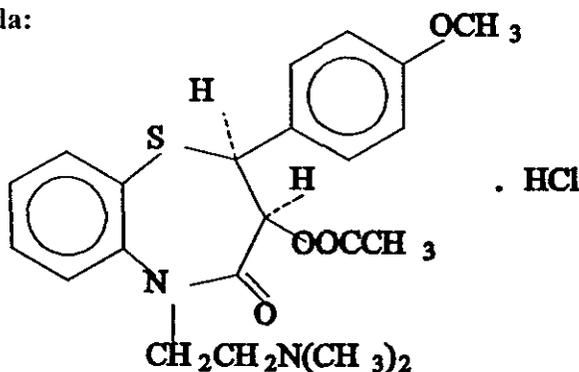
Chemical Name:

cis-(+)-3-Acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride.

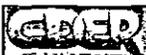
Molecular Formula: $C_{22}H_{26}N_2O_4S \cdot HCl$

Molecular Weight: 450.99

Structural Formula:



Diltiazem Hydrochloride



CHEMISTRY REVIEW



Chemistry Review Data Sheet

A. DMFs: Raw Materials

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II		Diltiazem Hydrochloride	3	Adequate	Nov, 30, 1999 L. Tang	Active
	II		Diltiazem Hydrochloride	3	Adequate	Feb. 14, 2000 S. Basaran	Active
	II			4	N/A		/
	II			4	N/A		
	II			4	N/A		/
	II			4	N/A		/
	II			3	Adequate	March 1, 2001 Dr. J. Salemme	
	II			4	N/A		/
	II			4	N/A		/
	II			4	N/A		/
	II			4	N/A		/

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)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. DMFs: Packaging Material

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	Sep. 15, 2000	Packaging Component
	II			3	Adequate	Sep. 22, 2000	\
	II			3	Adequate	March 22, 2001	Packaging Component
	II			3	Adequate	Dec. 05, 1999 Nov. 23, 1994	Closure
	II			3	Adequate	Sep. 22, 1997	Closure
	II			3	Adequate	April 01, 1993	Packaging Component
	II			3	Adequate	Aug. 20, 2001	Packaging Component
	II			3	Adequate	March 13, 1996	\
	II			3	Adequate	Feb. 3, 2002	\
	II			3	Sufficient	March 06, 1995	Packaging Component
	II			3	Adequate	Oct. 30, 1997	Packaging Component

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)

17. RELATED/SUPPORTING DOCUMENTS:

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,787	Cardizem — (Diltiazem HCl) IND for 180 and 240 mg tablets - Biovail
NDA	20-939	Diltiazem HCl, Extended Release Capsules, 120, 180, 240 and 300 mg, Biovail



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS::

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A (No statistical analysis of the stability data)		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Pending		
LNC	N/A		
Methods Validation	To be submitted		
DMETS	Pending		
EA	Not Acceptable		
Microbiology	N/A		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.

Yes No If no, explain reason(s) below:

The Chemistry Review for NDA 21-392

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Some additional deficiencies related to the new strengths have been identified in this review. The resolution of these deficiencies should be relatively straight forward since most of them involve inadequate documentation by the applicant. A list of deficiencies has been sent to the applicant by FAX on May 21, 2002 and applicant will be responding to these deficiencies shortly. A recommendation on approvability cannot be given at this time since the inspection status of one manufacturing facility is still pending

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 and Drug Substance

- Diltiazem Hydrochloride USP is a well known active ingredient and is listed in USP. Diltiazem Hydrochloride drug substance has two chiral centers and is manufactured by [redacted] Diltiazem Hydrochloride is freely soluble in Chloroform, Methanol, and Water and slightly soluble in Ethanol. For details on the structure, manufacture, and sources of Diltiazem Hydrochloride drug substance, the applicant provided references to two DMF #'s [redacted] These DMFs have been reviewed and found to be satisfactory. Based on the drug substance stability data a [redacted] retest date for drug substance has been assigned.
- Diltiazem Hydrochloride Extended Release Tablets are intended for once-daily administration. Pharmacokinetic data from two studies demonstrated that Diltiazem Hydrochloride Extended Release Tablets are bioequivalent to Diltiazem Hydrochloride Extended Release Capsules approved in the applicant's NDA 20-939. The mechanism of the extended release tablets involves beads containing the active and inactive ingredients [redacted]
[redacted] The beads are combined with other excipients and compressed into tablets.
- The applicant submitted another NDA [redacted] (Cardizem [redacted], dated August 23, 2001 which was converted to a major amendment to pending NDA 21-392 (this NDA.). The reason is that the drug formulation in both NDAs is the same [redacted]

The Clinical Division therefore decided that — should be nothing more than an amendment to [] and the applicant agreed to this.

- The application has been amended (11 Jan., 2002) to include additional strengths of 120 mg, 180 mg, and 420 mg Extended Release Tablets. The previously approved Diltiazem HCl Extended Release Capsules NDA 20-939 has 120 mg and 180 mg strengths but does not have any strength equivalent to 420 mg tablets.
- Based on — updated data for 240 mg, 300 mg, and 360 mg and a very limited data for 120 mg, 180 mg, and 420 mg tablets an expiration date beyond — for all strengths can not be assigned.

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

The product is proposed to be used for the treatment of hypertension, it may be used alone or in combination with other antihypertensive medications. Its pharmacology, pharmacokinetics, therapeutic efficacy and safety profile is well known. The Diltiazem Hydrochloride Extended Release Tablets 120 mg, 180 mg, 240 mg, 300 mg, 360 mg, and 420 mg are intended for once-daily administration. According to applicant, Clinical trials have studied doses 120 mg to 540 mg administered once-daily at bedtime and in the morning. []

]

C. Basis for Approvability or Not-Approval Recommendation

A list of the deficiencies which should be addressed is attached at the end of this review. A copy of the deficiencies from review #1 and this review #2 was sent to the applicant by Fax on May 21, 2002. The applicant will be responding to these deficiencies shortly. A recommendation of approvability can not be given at this time since an overall recommendation from Office Of Compliance regarding cGMP status of facilities submitted for inspection is pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

22 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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

/s/

Ramsharan Mittal
6/5/02 06:34:32 PM
CHEMIST

Kasturi Srinivasachar
6/5/02 06:50:27 PM
CHEMIST

NDA 21-392

**Diltiazem Hydrochloride
Extended-Release Tablets**

Biovail Laboratories Incorporated

**Ramsharan D. Mittal
Division of Cardio-Renal Drug Products**

Chemistry Review Data Sheet

1. NDA 21-392
2. REVIEW #: 1
3. REVIEW DATE: 22-MAY-2002
4. REVIEWER: Ramsharan D. Mittal
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

N000

08-JUN-2001

N000-AZ

22-AUG-2001

N-BC

17-OCT-2001

7. NAME & ADDRESS OF APPLICANT:

Name: Biovail Laboratories Incorporated

Address: Chelston Park Building 2
Collymore Rock, St. Michael BHI, Barbados WI

Representative: John B. Dubeck (U.S. Agent)

Telephone: 202-434-4125

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cardizem —

b) Non-Proprietary Name (USAN): Diltiazem Hydrochloride Extended Release Tablets

c) Code Name/# (ONDC only):

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

CHEMISTRY REVIEW

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL. CATEGORY: Calcium Channel Blocker
11. DOSAGE FORM: Extended Release Tablets
12. STRENGTH/POTENCY: 240 mg, 300 mg and 360 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, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA:

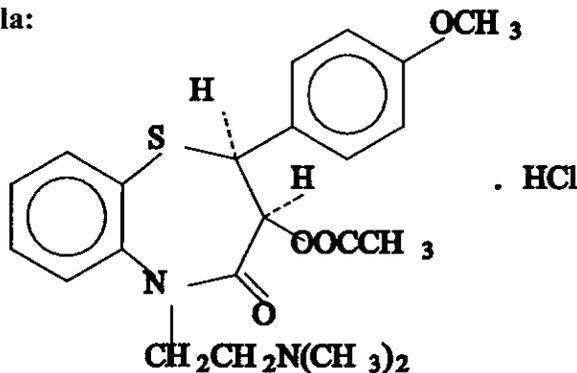
Chemical Name:

cis-(+)-3-Acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride.

Molecular Formula: $C_{22}H_{26}N_2O_4S \cdot HCl$

Molecular Weight: 450.99

Structural Formula:



Diltiazem Hydrochloride

CHEMISTRY REVIEW

Chemistry Review Data Sheet

A. DMFs: Raw Materials

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
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	II			4	N/A		
	II			4	N/A		
	II			4	N/A		
	II			4	N/A		
	II			3	Adequate	March 1, 2001 Dr. J. Salemme	
	II			4	N/A		
	II			4	N/A		
	II			4	N/A		
	II			4	N/A		

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)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

B. DMFs: Packaging Material

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	Sep. 15, 2000	Packaging Component
	II			3	Adequate	Sep. 22, 2000	—
	II			3	Adequate	March 22, 2001	Packaging Component
	II			3	Adequate	Dec. 05, 1999 Nov. 23, 1994	Closure
	II			3	Adequate	Sep. 22, 1997	Closure
	II			3	Adequate	April 01, 1993	Packaging Component
	II			3	Adequate	Aug. 20, 2001	Packaging Component
	II			3	Adequate	March 13, 1996	—
	II			3	Adequate	Feb. 3, 2002	—
	II			3	Sufficient	March 06, 1995	Packaging Component
	II			3	Adequate	Oct. 30, 1997	Packaging Component

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

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5 – Authority to reference not granted

6 – DMF not available

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17. RELATED/SUPPORTING DOCUMENTS:

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,787	Cardizem — (Diltiazem HCl) IND for 180 and 240 mg tablets - Biovail
NDA	20-939	Diltiazem HCl, Extended Release Capsules, 120, 180, 240 and 300 mg, Biovail

CHEMISTRY REVIEW

Chemistry Review Data Sheet

18. STATUS::

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A (No statistical analysis of the stability data)		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Pending		
LNC	N/A		
Methods Validation	To be submitted		
DMETS	Pending		
EA	Not Acceptable		
Microbiology	N/A		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.

___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-392

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The chemistry section is deficient in numerous areas of manufacturing and controls. The resolution of these deficiencies should be relatively straight forward since most of them involve inadequate documentation by the applicant. A list of deficiencies has been sent to the applicant by FAX on May 21, 2002 and applicant will be responding to these deficiencies shortly. A recommendation on approvability cannot be given at this time since the inspection status of one manufacturing facility is still pending

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 and Drug Substance

- Diltiazem Hydrochloride USP is a well known active ingredient and is listed in USP. Diltiazem Hydrochloride drug substance has two chiral centers and is manufactured by [redacted] Diltiazem Hydrochloride is freely soluble in Chloroform, Methanol, and Water and slightly soluble in Ethanol. For details on the structure, manufacture, and sources of Diltiazem Hydrochloride drug substance, the applicant provided references to two DMF #'s. [redacted] These DMFs have been reviewed and found to be satisfactory. Based on the drug substance stability data a retest date for drug substance has been assigned.
- Diltiazem Hydrochloride Extended Release Tablets are intended for once-daily administration. Pharmacokinetic data from two studies demonstrated that Diltiazem Hydrochloride Extended Release Tablets are bioequivalent to Diltiazem Hydrochloride Extended Release Capsules approved in the applicant's NDA 20-939. The mechanism of the extended release tablets involves beads containing the active and inactive ingredients [redacted]
[redacted] The beads are combined with other excipients and compressed into tablets.
- The applicant submitted another NDA [redacted] (Cardizem [redacted] dated August 23, 2001 which was converted to a major amendment to pending NDA 21-392 (this NDA.). The reason is that the drug formulation in both NDAs is the same and the difference between the two applications is in the time of administration of the

drug. The Clinical Division therefore decided that it should be nothing more than an amendment to the NDA and the applicant agreed to this.

- The first group of drug product batches in this NDA are referred to as Bio (Clinical) Batches. As per meeting with FDA, a manufacturing matrix was implemented whereby two 240 mg batches, one 300 mg batch and two 360 mg batches were manufactured in support of this NDA. The first 360 mg batch manufactured is the batch used for bio-equivalence studies.
- The stability data is very limited and more stability data is needed to assign a meaningful expiration date.

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

The product is proposed to be used for the treatment of hypertension, it may be used alone or in combination with other antihypertensive medications. Its pharmacology, pharmacokinetics, therapeutic efficacy and safety profile is well known. The Diltiazem Hydrochloride Extended Release Tablets 240 mg, 300 mg, and 360 mg are intended for once-daily administration. According to applicant, Clinical trials have studied doses 120 mg to 540 mg administered once-daily at bedtime and in the morning.

The Diltiazem Hydrochloride Extended Release Tablets 240 mg and 360 mg tablets are scored and can be divided to deliver half the dose.

C. Basis for Approvability or Not-Approval Recommendation

A list of the deficiencies which should be addressed is attached at the end of this review. A copy of the deficiencies from this review #1 was sent to the applicant by Fax on May 21, 2002. The applicant will be responding to these deficiencies shortly. A recommendation of approvability can not be given at this time since an overall recommendation from Office Of Compliance regarding cGMP status of facilities submitted for inspection is pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

42 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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

/s/

Ramsharan Mittal
6/5/02 02:40:13 PM
CHEMIST

Kasturi Srinivasachar
6/5/02 06:42:20 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21392/000 Action Goal:
Stamp: 11-JUN-2001 District Goal: 12-MAY-2002
Regulatory Due: 11-JUL-2002 Brand Name: DILTIAZEM HCL EXTENDED RELEASE TABLETS
Applicant: BIOVAIL LABS Estab. Name:
Priority: 110 Generic Name: DILTIAZEM HCL EXTENDED RELEASE TABLETS
Org Code: Dosage Form: (EXTENDED-RELEASE TABLET)
Strength: 240 MG, 300 MG, 360 MG

Application Comment: BIOVAIL LABS INC, CAROLINA, PUERT RICO, MANUFACTURES IMMEDIATE RELEASE BEADS AND COATED BEADS.

BIOVAIL, STEINBACH, MANITOBA, CANADA, ALSO RESPONSIBLE FOR PACKGING IN — BOTTLES.

BIOVAIL TECHNOLOGIES LIMITED, 3701 COCORD PARKWAY, CHANTILY, VIRGINIA 20151 IOS RESPONSIBLE FOR MANUFACTURE OF BEADS. THERE WAS NO CFN NUMBER FOR THIS FACILITY AND IT WAS NOT ENTERED IN THE LIST OF ESTABLISHMENTS.
BIOVAIL TECHNOLOGIES LIMITED, CHANTILY, VIRGINIA, MANUFACTURES BEADS.

BIOVAIL CORPORATION, STEINBACH, MANITOBA, CANADA IS THE MANUFACTURER OF COATED BEADS, UNCOATED AND COATED TABLETS, PACKAGING IN BPTTLES AND RELEASE OF PRODUCT AND STABILITY TESTING.

(on 22-JUL-2001 by R. MITTAL (HFD-110) 301-594-5353)

FDA Contacts: ID = 127376 , Project Manager
R. MITTAL (HFD-110) 301-594-5353 , Review Chemist
K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation: ACCEPTABLE on 29-MAY-2002 by S. ADAMS (HFD-324) 301-594-0095
ACCEPTABLE on 23-JAN-2002 by GARCIA M

Establishment: [

DMF No: AADA:
Responsibilities:]
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JUL-2001				MITTAL R
OC RECOMMENDATION	23-JUL-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIO J

Establishment: 2650179
BIOVAIL LABORATORIES INC
AVE 34 ITURREGUI CORNER TO B ST
CAROLINA, PR 00984

DMF No: AADA:
Responsibilities: INTERMEDIATE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Profile: CRU OAI Status: NONE
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JUL-2001				MITTALR
OC RECOMMENDATION	23-JUL-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: 9615235
 BIOVAIL LIFESCIENCES ✓
 STEINBACH, MANITOBA, CA

DMF No: AADA:
 Responsibilities: FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Profile: TTR OAI Status: NONE
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JUL-2001				MITTALR
SUBMITTED TO DO	23-JUL-2001	GMP			EGASM
ASSIGNED INSPECTION	27-JUL-2001	GMP			EGASM
INSPECTION SCHEDULED	07-NOV-2001		09-NOV-2001		IRIVERA
INSPECTION PERFORMED	19-NOV-2001		08-NOV-2001		IRIVERA
DO RECOMMENDATION	17-JAN-2002			ACCEPTABLE	GARCIAI
OC RECOMMENDATION	17-JAN-2002			INSPECTION ACCEPTABLE DISTRICT RECOMMENDATION	GARCIAI

Establishment: 1125566
 BIOVAIL TECHNOLOGIES ✓
 3701 CONCORDE PKWY SUITE 100
 CHANTILLY, VA 20151

DMF No: AADA:
 Responsibilities: INTERMEDIATE MANUFACTURER

Profile: TTR OAI Status: NONE

Estab. Comment: THE FACILITY AT CHANTILLY, VA, MANUFACTURES [] BEADS FOR THE DILTIAZEM HYDROCHLORIDE TABLETS. THE [] BEADS ARE USED IN THE MANUFACTURE OF DRUG PRODUCT []
] BY MISTAKE, THIS FACILITY WAS NOT ENTERED IN THE ORIGINAL EER. (on 13-MAR-2002 by R. MITTAL (HFD-110) 301-594-5353)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	13-MAR-2002				MITTALR
SUBMITTED TO DO	13-MAR-2002	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	18-MAR-2002	GMP			MGARCIAI
INSPECTION SCHEDULED	18-MAR-2002		05-APR-2002		WBARGO
INSPECTION PERFORMED	30-APR-2002		10-APR-2002		WBARGO

123102 This inspection of a pharmaceutical manufacturer was initiated in response to assignments from HFD-324 requesting pre-approval inspections related to NDAs 21-392, Diltiazem delayed release tablets, []

In addition, this inspection covered a full-GMP evaluation. The inspection was conducted under C.P. 7346.832 and 7356.002, and designated with FACTS Assignment ID: 890565 and Operation ID: 726626. This was the initial inspection at this facility.

During this inspection, the data to support the application was reviewed for

authenticity and included: manufacturing, raw material testing, finished product testing, method validation, and stability.

[

DO RECOMMENDATION	28-MAY-2002	ACCEPTABLE	MGARCIA1
OC RECOMMENDATION	29-MAY-2002	INSPECTION ACCEPTABLE	ADAMSS DISTRICT RECOMMENDATION

Establishment: [

DMF No:	AADA:
Responsibilities: []
Profile:	OAI Status: NONE
Estab. Comment:	

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JUL-2001				MITTALR
OC RECOMMENDATION	23-JUL-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: [

DMF No:	AADA:
Responsibilities: []
Profile: CSN	OAI Status: NONE
Estab. Comment:	

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JUL-2001				MITTALR
SUBMITTED TO DO	23-JUL-2001	GMP			EGASM
DO RECOMMENDATION	27-JUL-2001			ACCEPTABLE BASED ON FILE REVIEW	EGASM

BASED ON EI OF 10/18/00

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

OC RECOMMENDATION 30-JUL-2001

ACCEPTABLE EGASM
DISTRICT RECOMMENDATION

Appears This Way
On Original

Appendix 1

On June 6, 2002, a Biovail representative contacted Nancy Sager, a Supervisory Chemist in the Quality Information Staff Division of the Office of Pharmaceutical Science, who explained that the FDA is more interested in seeing Environmental Assessments for new indications which expand the patient pool as opposed to new formulations that companies may use to acquire a larger share of the existing patient pool. She stated that the 21 CFR 25.31 (a) categorical exemption applies with regard to Biovail's Diltiazem Hydrochloride Extended Release Tablets because the applicant is attempting to bring patients on other dosage forms to their new dosage form. Therefore, as agreed with Dr. Ramsharan Mittal, the Chemistry Reviewer for this product, an Environmental Assessment of the effects of this new dosage form will not be conducted and the Environmental Impact Analysis Statement filed in the original submission stands.

Appears This Way
On Original