CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-800

CHEMISTRY REVIEW(S)

NDA 20-800

TwinJect™

Hollister-Stier Laboratories LLC

Chong Ho Kim, Ph.D.

Division of Pulmonary and Allergy Drug Products

Chemistry Review Data Sheet

1. NDA #: 20-800

2. REVIEW #: 10

3. REVIEW DATE: 19-DECEMBER-2002

4. REVIEWER: Chong Ho Kim, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	05-DEC-96
Amendment [BZ]	10-JAN-97
Amendment [BC]	10-JAN-97
Amendment [BZ]	14-FEB-97
Amendment [BC]	03-APR-97
Amendment [BC]	09-APR-97
Amendment [BC]	29-MAY-97
Amendment [BC]	05-SEP-97
Amendment [BZ]	01-OCT-97
Amendment [BC]	10-NOV-97
Amendment [AC]	29-MAY-98
Amendment [BZ]	17-JUN-98
Amendment [BC]	16-JUL-98
Amendment [BC]	24-AUG-98
Amendment [AC]	16-AUG-99
Amendment [BC]	13-DEC-99
Amendment [AZ]	21-APR-00
Amendment [BC]	29-MAR-01
Amendment [AZ]	26-JUN-01
Amendment [BC]	17-JUL-01
Amendment [BC]	15-AUG-01
Amendment [BC]	28-SEP-01
Amendment [BC]	29-OCT-01
Amendment [AZ]	26-JUL-02
Amendment [BC]	24-SEP-02
Amendment [BC]	25-SEP-02
Amendment [BC]	04-NOV-02
Amendment [BC]	18-NOV-02

CHEMISTRY REVIEW

Chemistry Assessment Section

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment[BC]	10-DEC-02

7. NAME & ADDRESS OF APPLICANT:

Name: Hollister-Stier Laboratories LLC

Address: 3525 North Regal Street
Spokane, WA 99207-5796

Representative: Mr. David L. Mirabell
Director of Regulatory Affairs

Telephone: 509-489-5656

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: TwinJect™
b) Nonproprietary Name (USAN): Epinephrine Injection, USP (1:1000)
c) Code Name/#:
d) Chem. Type/Submission Priority:
- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Adrenergic

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY:
Each unit may deliver two doses of 0.3 mL each.

13. ROUTE OF ADMINISTRATION: Subcutaneous or Intramuscular

14. Rx/OTC DISPENSED: x Rx __OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note20]:

_____SPOTS product – Form Completed

Chemistry Assessment Section

X Not a SPOTS product

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

Epinephrine, USP
[Adrenaline is BAN; Epinephrine Hydrochloride is JAN]

For structure, see "USP Dictionary of USAN and International Drug Names".

Chemical Name: 1,2-Benzenediol, (R)- 4-[1-hydroxy-2-(methylamino)ethyl]-1,2-benzenediol.

CAS Number: [51-43-4]

Molecular Formula: $C_9H_{13}NO_3$

Molecular Weight: 183.21

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
[redacted]	II	[redacted]	[redacted]	3	Adequate	8/14/98	
[redacted]	III	[redacted]	[redacted]	3	Adequate	6/10/99	reviewed by Dr. Hathaway
[redacted]	III	[redacted]	[redacted]	3	Inadequate*	10/10/01	Reviewed by Dr. Lostritto

*Information was provided in the NDA, and adequate for this application.

[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)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Unnecessary
EER	ds and dp sites and testing laboratories	10/1/02	pending (11/25/02)	
Pharm/Tox				*
Biopharm	N/A			
LNC	N/A			
Methods Validation				**
OPDRA	acceptability of the trade name		7/11/00	Acceptable (TwinJect)
EA	exclusion requested			Acceptable
Microbiology	Response	9/18/02	Adequate (10/18/02)	

*Discussed with Dr. Sun regarding the [redacted]. The tentative limits are based on the applicant's limited data.

**Three copies of MV packages were provided.

Chemistry Assessment Section

The Chemistry Review for NDA 20-800

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA may be approved pending on a satisfactory EER.

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

[redacted]

II. Summary of Chemistry Assessments

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

1). The epinephrine drug substance is manufactured by [redacted] (DMF #' [redacted] The DMF is adequate to support the current NDA.

2). TwinJect™ [Epinephrine Injection, USP (1:1000)] is a drug delivery system consisting of an automatic needle insertion/injection device and a [redacted] by Abbott Laboratories.

3). It is stated that the mode of action of this product is similar to other auto-injectors. It has two unique features, the [redacted] which provides a precise dose and the [redacted] which allows a second measured dose.

4). The test methods for drug substance and for the drug product are acceptable. **Applicant has provided three copies of method validation packages and method validation will be requested shortly.**

5). **EER for all drug product manufacturing, packaging and testing facilities are pending as of December 19, 2002.**

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

The TwinJect™ Epinephrine Injection is designed to deliver two doses of 0.3mL each. The first dose is by auto-Injector, while the second dose is delivered manually after dismantle of the device.

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable. However, acceptable EER should be obtained from OC to gain approval. The Phase IV commitment/ agreements on page 6 should be conveyed to the applicant in the approval letter.

III. Administrative

A. Reviewer's Signature

Chong Ho Kim

B. Endorsement Block

ChemistName/Date:	Chong Ho Kim/ 19-DEC-2002
ChemistryTeamLeaderName/Date:	Guirag Poochikian/
ProjectManagerName/Date:	Ladan Jafari/

C. CC Block

Orig. NDA #20-800
HFD-570/Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/LJafari
R/D Init. by:

Doc: n20-800r10.D19

47 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/

Chong-Ho Kim
12/2/02 04:00:35 PM
CHEMIST
The list of chemistry deficiencies and comments on page 40 should be conveyed to the applicant.

Guiragos Poochikian
12/3/02 05:36:37 PM
CHEMIST

Chemistry Review Data Sheet

NDA 20-800

TwinJect™

Hollister-Stier Laboratories LLC

Chong Ho Kim, Ph.D.

Division of Pulmonary and Allergy Drug Products

Chemistry Review Data Sheet

1. NDA #: 20-800

2. REVIEW #: 9

3. REVIEW DATE: 02-DECEMBER-2002

4. REVIEWER: Chong Ho Kim, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	05-DEC-96
Amendment [BZ]	10-JAN-97
Amendment [BC]	10-JAN-97
Amendment [BZ]	14-FEB-97
Amendment [BC]	03-APR-97
Amendment [BC]	09-APR-97
Amendment [BC]	29-MAY-97
Amendment [BC]	05-SEP-97
Amendment [BZ]	01-OCT-97
Amendment [BC]	10-NOV-97
Amendment [AC]	29-MAY-98
Amendment [BZ]	17-JUN-98
Amendment [BC]	16-JUL-98
Amendment [BC]	24-AUG-98
Amendment [AC]	16-AUG-99
Amendment [BC]	13-DEC-99
Amendment [AZ]	21-APR-00
Amendment [BC]	29-MAR-01
Amendment [AZ]	26-JUN-01
Amendment [BC]	17-JUL-01
Amendment [BC]	15-AUG-01
Amendment [BC]	28-SEP-01
Amendment [BC]	29-OCT-01

Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment[AZ]	26-JUL-02
Amendment[BC]	24-SEP-02
Amendment[BC]	25-SEP-02
Amendment[BC]	04-NOV-02
Amendment[BC]	18-NOV-02

7. NAME & ADDRESS OF APPLICANT:

Name:	Hollister-Stier Laboratories LLC
Address:	3525 North Regal Street Spokane, WA 99207-5796
Representative:	Mr. David L. Mirabell Director of Regulatory Affairs
Telephone:	509-489-5656

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: TwinJect™
b) Nonproprietary Name (USAN): Epinephrine Injection, USP (1:1000)
c) Code Name/#:
d) Chem. Type/Submission Priority:
- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Adrenergic

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY:
Each unit may deliver two doses of 0.3 mL each.

13. ROUTE OF ADMINISTRATION: Subcutaneous or Intramuscular

14. Rx/OTC DISPENSED: x Rx __ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note20]:
_____SPOTS product – Form Completed

Chemistry Review Data Sheet

___X___Not a SPOTS product

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

Epinephrine, USP
[Adrenaline is BAN; Epinephrine Hydrochloride is JAN]

For structure, see "USP Dictionary of USAN and International Drug Names".

Chemical Name: 1,2-Benzenediol,(R)- 4-[1-hydroxy-2-(methylamino)ethyl]-1,2-benzenediol.

CAS Number: [51-43-4]

Molecular Formula: $C_9H_{13}NO_3$

Molecular Weight: 183.21

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
—	II			3	Adequate	8/14/98	
—	III	/	/	3	Adequate	6/10/99	reviewed by Dr. Hathaway
—	III			3	Inadequate*	10/10/01	Reviewed by Dr. Lostritto

*Information was provided in the NDA. and adequate for this application.

[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)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

Chemistry Review Data Sheet

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Unnecessary
EER	ds and dp sites and testing laboratories	10/1/02	pending (11/25/02)	
Pharm/Tox				*
Biopharm	N/A			
LNC	N/A			
Methods Validation				**
OPDRA	acceptability of the trade name		7/11/00	Acceptable (TwinJect)
EA	exclusion requested			Acceptable
Microbiology	Response	9/18/02	Adequate (10/18/02)	

***Discussed with Dr. Sun regarding the the applicant's limited data. The tentative limits are based on**

****Applicant should provide three copies of method validation package, once we reach agreement on the specifications.**

Executive Summary Section

The Chemistry Review for NDA 20-800

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable from a CMC standpoint.

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

None

II. Summary of Chemistry Assessments

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

1). The epinephrine drug substance is manufactured by — (DMF —. The DMF is adequate to support the current NDA.

2). TwinJect™ [Epinephrine Injection, USP (1:1000)] is a drug delivery system consisting of an automatic needle insertion/injection device and a — by Abbott Laboratories.

3). It is stated that the mode of action of this product is similar to other auto-injectors. It has two unique features, the — which provides a precise dose and the — which allows a second measured dose.

4). The test methods for drug substance and for the drug product are acceptable. However, no agreement is reached for specifications. **Applicant should provide new copies of method validation packages, once the remaining issues are resolved.**

5). EER for all drug product manufacturing, packaging and testing facilities are pending as of November 25, 2002.

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

The TwinJect™ Epinephrine Injection is designed to deliver two doses of 0.3mL each. The first dose is by auto-Injector, while the second dose is delivered manually after dismantle of the device.

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable. However, the pending

deficiencies listed at the end of this review should be addressed and acceptable EER should be obtained from OC to gain approval.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:	Chong Ho Kim/ 02-DEC-2002
ChemistryTeamLeaderName/Date:	Guirag Poochikian/
ProjectManagerName/Date:	Ladan Jafari/

C. CC Block

Orig. NDA #20-800
HFD-570/Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/LJafari
R/D Init. by:

Doc: n20-800r9.D02

33 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/

Chong-Ho Kim
12/2/02 04:00:35 PM
CHEMIST
The list of chemistry deficiencies and comments on page 40 should be conveyed to the applicant.

Guiragos Poochikian
12/3/02 05:36:37 PM
CHEMIST

Division of Pulmonary and Allergy Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-800 **CHEM. REVIEW #**: 8 **REVIEW DATE**: December 7, 2001

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	05-DEC-96	06-DEC-96	16-DEC-96
Amendment [BZ]	10-JAN-97	13-JAN-97	22-JAN-97
Amendment [BC]	10-JAN-97	13-JAN-97	22-JAN-97
Amendment [BZ]	14-FEB-97	18-FEB-97	25-FEB-97
Amendment [BC]	03-APR-97	09-APR-97	15-APR-97
Amendment [BC]	09-APR-97	10-APR-97	15-APR-97
Amendment [BC]	29-MAY-97	30-MAY-97	04-JUN-97
Amendment [BC]	05-SEP-97	08-SEP-97	11-SEP-97
Amendment [BZ]	01-OCT-97	02-OCT-97	08-OCT-97
Amendment [BC]	10-NOV-97	12-NOV-97	18-NOV-97
Amendment [AC]	29-MAY-98	01-JUN-98	09-JUN-98
Amendment [BZ]	17-JUN-98	19-JUN-98	23-JUN-98
Amendment [BC]	16-JUL-98	17-JUL-98	22-JUL-98
Amendment [BC]	24-AUG-98	25-AUG-98	27-AUG-98
Amendment [AC]	16-AUG-99	17-AUG-99	23-AUG-99
Amendment [BC]	13-DEC-99	15-DEC-99	27-DEC-99
Amendment [AZ]	21-APR-00	24-APR-00	27-APR-00
Amendment [BC]	29-MAR-01	30-MAR-01	02-APR-01
Amendment [AZ] *	26-JUN-01	28-JUN-01	28-JUN-01
Amendment [BC] *	17-JUL-01	18-JUL-01	18-JUL-01
Amendment [BC] *	15-AUG-01	16-JUL-01	16-AUG-01
Amendment [BC] *	28-SEP-01	01-OCT-01	02-OCT-01
Amendment [BC] *	29-OCT-01	30-OCT-01	31-OCT-01

*Subject of this review.

NAME AND ADDRESS OF APPLICANT:

Hollister-Stier Laboratories LLC
3525 orth Regal Street
Spokane, WA 99207-5796

ATTN: David L. Mirabell
Director
Regulatory Affairs
Tel: (509) 489-5656

DRUG PRODUCT NAME:

Proprietary: TwinJect™
Nonproprietary/USAN: Epinephrine Injection,USP (1:1000)

Code Name/#:
Chem. Type/Ther. Class: 3S
Established Name of Drug Substance:
Epinephrine: 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethanol

PHARMACOL. CATEGORY/INDICATION: Adrenergic

DOSAGE FORM: Injection

STRENGTHS: ____ (1:1000)
Each unit may deliver two doses of 0.3 mL each.

Microbiologist stated that the amendment is approvable, however, the microbiologist's comments are listed in the deficiency comments.

REMARKS/COMMENTS:

1. Methods validation by the Agency will be deferred pending resolution of deficiencies in the methods.

CONCLUSION AND RECOMMENDATION:

This NDA is considered to be not approvable from CMC standpoint. The outstanding deficiencies be addressed adequately.

Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc:
Orig. NDA #20-800
HFD-570 Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/RNicklas
HFD-570/JSun
HFD-570/LJafari
R/D Init. By:

doc. NDA 20-800r8.D07

Review Notes:

45 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/

Chong-Ho Kim
12/10/01 08:52:03 AM
CHEMIST

Guiragos Poochikian
12/11/01 01:07:39 PM
CHEMIST

- JAHAc'

JUL 14 2000

Division of Pulmonary Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-800 **CHEM. REVIEW #:** 6 **REVIEW DATE:** July 13, 2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	05-DEC-96	06-DEC-96	16-DEC-96
Amendment [BZ]	10-JAN-97	13-JAN-97	22-JAN-97
Amendment [BC]	10-JAN-97	13-JAN-97	22-JAN-97
Amendment [BZ]	14-FEB-97	18-FEB-97	25-FEB-97
Amendment [BC]	03-APR-97	09-APR-97	15-APR-97
Amendment [BC]	09-APR-97	10-APR-97	15-APR-97
Amendment [BC]	29-MAY-97	30-MAY-97	04-JUN-97
Amendment [BC]	05-SEP-97	08-SEP-97	11-SEP-97
Amendment [BZ]	01-OCT-97	02-OCT-97	08-OCT-97
Amendment [BC]	10-NOV-97	12-NOV-97	18-NOV-97
Amendment [AC]	29-MAY-98	01-JUN-98	09-JUN-98
Amendment [BZ]	17-JUN-98	19-JUN-98	23-JUN-98
Amendment [BC]	16-JUL-98	17-JUL-98	22-JUL-98
Amendment [BC]	24-AUG-98	25-AUG-98	27-AUG-98
Amendment [AC]	16-AUG-99	17-AUG-99	23-AUG-99
Amendment [BC]	13-DEC-99	15-DEC-99	27-DEC-99
Amendment [AZ]*	21-APR-00	24-APR-00	27-APR-00

*Subject of this review.

NAME AND ADDRESS OF APPLICANT:

Hollister-Stier Laboratories LLC
P.O.Box 3145
Spokane, WA 99220-3145

ATTN: David L. Mirabell
Manager
Regulatory Affairs
Tel: (509) 489-5656

DRUG PRODUCT NAME:

Proprietary: TwinJect™ Epinephrine Injection, USP (1:1000)
Nonproprietary/USAN: Epinephrine Injection
Code Name/#:
Chem. Type/Ther. Class: 3S
Established Name of Drug Substance:
Epinephrine: 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethanol

PHARMACOL. CATEGORY/INDICATION: Adrenergic

DOSAGE FORM: Injection

STRENGTHS: (1:1000)
Each unit may deliver two doses of 0.3 mL each.

ROUTE OF ADMINISTRATION: Subcutaneous or Intramuscular

Rx/OTC: Prescription

SPECIAL PRODUCT: No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

Epinephrine, USP. $C_9H_{13}NO_3$.
[Adrenaline is BAN; Epinephrine Hydrochloride is JAN]
1,2-Benzenediol,(R)- 4-[1-hydroxy-2-(methylamino)ethyl]-1,2-benzenediol. CAS-51-43-4

For structure, see "USP Dictionary of USAN and International Drug Names".

SUPPORTING DOCUMENTS:

DMFs:

DMF Number	Holder	Subject	Status	Date Reviewed	Referenced Section in the NDA
[redacted]	[redacted]	[redacted]	adequate	8/14/98	3.2
[redacted]	[redacted]	[redacted]	adequate	3/11/97	3.3
[redacted]	[redacted]	[redacted]	adequate	6/21/00	Response 2 (Amendment dated 8/16/99)
[redacted]	[redacted]	[redacted]	adequate	6/10/99 by Dr. Hathaway	"
[redacted]	[redacted]	[redacted]	adequate	2/2/96 by Dr. Shaw	"
[redacted]	"	[redacted]	adequate	1/17/00	"
[redacted]	"	[redacted]	adequate	1/15/00	"

CONSULTS:

1. The new proposed trademark names for the Bayer auto-injector are: [redacted] and TwinJect™. The applicant has chosen [redacted]. However, Trademark Consult objected the [redacted] (only **TwinJect™** is acceptable). OPDRA notified that the proposed trademark name "TwinJect" is acceptable (7/11/00).

2. A final update request of EER was filed on **June 14, 2000** for all facilities involved in synthesis, release and stability testing of drug substance and manufacturing, packaging, in-process testing, release and stability testing of drug products. Two sites are acceptable. However, [redacted] is on " **OAI Alert**" and EER is " withhold" as of June 17, 2000.

3. Biometrics consult for the proposed expiration dating period is not necessary. *Applicant claims that the stability data provided with the Auto-Injector assures the expiration dating period of the* [redacted]. The Proposed Shelf Life of the TwinJect is [redacted] from the date of epinephrine manufacture, i.e., [redacted] manufacture. The [redacted] contains [redacted] mg of epinephrine per mL of formulation ([redacted]

The initial assay values were ca. [redacted] however assay values were [redacted] range [redacted] and [redacted] at room temperature. It should be confirmed with the applicant that the proposed expiration dating period is from the date of [redacted] manufacture and should be reduced to [redacted]

4. Pharm/Tox consult request for [redacted] was requested on July 7, 2000 (result is pending).

REMARKS/COMMENTS:

1. Methods validation by the Agency will be deferred pending resolution of deficiencies in the methods.

2. Proposed limits for [redacted] in Response 1 should be evaluated by Pharm/Tox reviewer.

3. [redacted] is on " OAI Alert" and EER is " withhold" as of June 17, 2000.

CONCLUSION AND RECOMMENDATION:

This NDA is considered to be approvable from CMC standpoint provided that the outstanding deficiencies be addressed adequately. The pharmacological and toxicological issues in comment #1 regarding the [redacted] should be addressed by a pharm/tox reviewer. The approval of this NDA is pending satisfactory EER.

/S/

Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc:
Orig. NDA #20-800
HFD-570 Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/RNicklas
HFD-570/JSun
HFD-570/LJafari
R/D Init. By /S/

doc. NDA 20-800.CR6b

13 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

For structure, see "USP Dictionary of USAN and International Drug Names".

SUPPORTING DOCUMENTS:

DMFs:

DMF Number	Holder	Subject	Status	Date Reviewed	Referenced Section in the NDA
[redacted]	[redacted]	[redacted]	adequate	8/14/98	3.2
[redacted]	[redacted]	[redacted]	adequate	3/11/97	3.3
[redacted]	[redacted]	[redacted]	Inadequate	1/13/00	Response 2 (Amendment dated 8/16/99)
[redacted]	[redacted]	[redacted]	adequate	6/10/99 by Dr. Hathaway	"
[redacted]	[redacted]	[redacted]	adequate	2/2/96 by Dr. Shaw	"
[redacted]	"	[redacted]	adequate	1/17/00	"
[redacted]	"	[redacted]	adequate	1/15/00	"

CONSULTS:

1. The new proposed trademark names for the Bayer auto-injector are: [redacted] and TwinJect™. The applicant has chosen [redacted]. However, Trademark Consult objected to the [redacted] (only TwinJect™ is acceptable).

2. A final update request of EER was filed on January 7, 2000 for all facilities involved in synthesis, release and stability testing of drug substance and manufacturing, packaging, in-process testing, release and stability testing of drug products. The [redacted] (Establishment # [redacted] and Bayer Corporation facility (Establishment # 3010477) were found acceptable, however [redacted] (Establishment # [redacted] is pending as of 1/7/00.

3. Biometrics consult for the proposed expiration dating period is not necessary; the stability data provided with the Auto-Injector confirms the expiration dating period of the [redacted] from the date of epinephrine manufacture for the TwinJect is proposed. The proposed expiration dating period for the TwinJect should be reduced to [redacted] from the manufacturing date of [redacted]. The [redacted] contains [redacted] of epinephrine per mL of formulation ([redacted]. The initial assay values were ca. [redacted] however assay values were [redacted] range after [redacted] storage at room temperature.

4. Pharm/Tox consult request for Response 1d ' — , is pending.

REMARKS/COMMENTS:

1. Methods validation by the Agency will be deferred pending resolution of deficiencies in the methods.

2. Response 1d should be evaluated by Pharm/Tox reviewer.

CONCLUSION AND RECOMMENDATION:

This NDA is considered to be approvable from CMC standpoint provided that the outstanding deficiencies are addressed adequately.

In addition, the pharmacological and toxicological issues in comment #1d regarding the — should be addressed by a pharm/tox reviewer and EER for ——— facility should be found acceptable(see consults, item #2 above).

/S/

Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc:
Orig. NDA #20-800
HFD-570 Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/RNicklas
HFD-570/JSun
HFD-570/AChen
HFD-570/LJafar
R/D Init. By /S/

doc. NDA 20-800r5b.doc

17 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

D-10YRY

OCT 21 1998

Division of Pulmonary Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-800 **CHEM. REVIEW #**: 4 **REVIEW DATE**: October 20, 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	05-DEC-96	06-DEC-96	16-DEC-96
Amendment [BZ]	10-JAN-97	13-JAN-97	22-JAN-97
Amendment [BC]	10-JAN-97	13-JAN-97	22-JAN-97
Amendment [BZ]	14-FEB-97	18-FEB-97	25-FEB-97
Amendment [BC]	03-APR-97	09-APR-97	15-APR-97
Amendment [BC]	09-APR-97	10-APR-97	15-APR-97
Amendment [BC]	29-MAY-97	30-MAY-97	04-JUN-97
Amendment [BC]	05-SEP-97	08-SEP-97	11-SEP-97
Amendment [BZ]	01-OCT-97	02-OCT-97	08-OCT-97
Amendment [BC]	10-NOV-97	12-NOV-97	18-NOV-97
Amendment [AC]*	29-MAY-98	01-JUN-98	09-JUN-98
Amendment [BZ]*	17-JUN-98	19-JUN-98	23-JUN-98
Amendment [BC]*	16-JUL-98	17-JUL-98	22-JUL-98
Amendment [BC]*	24-AUG-98	25-AUG-98	27-AUG-98

*Subject of this review.

NAME AND ADDRESS OF APPLICANT:

Bayer Corporation
Pharmaceutical Division
3525 North Regal Street
Spokane, WA 99208

ATTN: David L. Mirabell
Manager
Regulatory Affairs
Tel:(509) 489-5656

DRUG PRODUCT NAME:

Proprietary: TwinJect™ Epinephrine Injection, USP (1:1000) [Previously

Nonproprietary/USAN: Epinephrine Injection

Code Name/#:

Chem. Type/Ther. Class: 3S

Established Name of Drug Substance:

Epinephrine: 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethanol

PHARMACOL. CATEGORY/INDICATION: Adrenergic

DOSAGE FORM: Injection

STRENGTHS: (1:1000)

ROUTE OF ADMINISTRATION: Subcutaneous or Intramuscular

Rx/OTC: Prescription

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

Epinephrine, USP. $C_9H_{13}NO_3$. 183.21
[Adrenaline is BAN; Epinephrine Hydrochloride is JAN]
1,2-Benzenediol, (R)- 4-[1-hydroxy-2-(methylamino)ethyl]-1,2-benzenediol. CAS-51-43-4

For structure, see "USP Dictionary of USAN and International Drug Names".

SUPPORTING DOCUMENTS:

DMFs:

DMF Number	Holder	Subject	Status	Date Reviewed	Referenced Section in the NDA
[redacted]	[redacted]	[redacted]	adequate	8/14/98	3.2
[redacted]	[redacted]	[redacted]	adequate	3/11/97	3.3

CONSULTS:

1. The new proposed trademark names for the Bayer auto-injector are: [redacted] and TwinJect™. The applicant has chosen [redacted]. However, Trademark Consult objected the [redacted] (only TwinJect™ is acceptable).

2. A final update request of EER was filed on September 9, 1997 for all facilities involved in synthesis, release and stability testing of drug substance and manufacturing, packaging, in-process testing, release and stability testing of drug products. The [redacted] (Establishment # [redacted] and [redacted] (Establishment # [redacted] were found acceptable, however Bayer Corporation facility (Establishment # 3010477) is pending as of 10/2/98.

3. Biometrics consult for the proposed expiration dating period is not necessary; the stability data provided with the Auto-Injector confirms the expiration dating period of the [redacted] Labeled Shelf Life of the TwinJect is [redacted] from the date of epinephrine manufacture. The [redacted] contains [redacted] of epinephrine per mL of formulation [redacted]. The initial assay values were ca. [redacted] however assay values were [redacted] range after [redacted] storage at room temperature.

REMARKS/COMMENTS:

1. Methods validation by the Agency will be deferred pending resolution of deficiencies in the methods.

2. Amendment[BZ] dated 6/17/98 contains information on CMC updates, performance evaluation, and labeling.

3. Amendment[BC] dated 7/16/98 contains the [redacted] performance testing and stability data on [redacted] lots of the drug product.

4. Amendment[BC] dated 8/24/98 contains product sample.

CONCLUSION AND RECOMMENDATION:

There is some outstanding deficiencies to be addressed. As we discussed in a team meeting dated October 20, 1998, the pharmacological and toxicological issues in comment #1 regarding the — should be addressed by a pharm/tox reviewer. This NDA is considered to be not approvable from CMC standpoint.

/S/

Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc:
Orig. NDA #20-800
HFD-570 Division File
HFD-570/CKim
HFD-570/GPoochikian
HFD-570/RNicklas
HFD-570/JSun
HFD-570/AChen
HFD-570/DTower
R/D Init. By /S/

doc. NDA 20-800.CR4

✓ Page(s) Withheld

25 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

NOV 20 1997

Division of Pulmonary Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-800 **CHEM. REVIEW #**: 3 **REVIEW DATE**: November 19, 1997

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	05-DEC-96	06-DEC-96	16-DEC-96
Amendment [BZ]	10-JAN-97	13-JAN-97	22-JAN-97
Amendment [BC]	10-JAN-97	13-JAN-97	22-JAN-97
Amendment [BZ]	14-FEB-97	18-FEB-97	25-FEB-97
Amendment [BC]	03-APR-97	09-APR-97	15-APR-97
Amendment [BC]	09-APR-97	10-APR-97	15-APR-97
Amendment [BC]	29-MAY-97	30-MAY-97	04-JUN-97
Amendment [BC]	05-SEP-97	08-SEP-97	11-SEP-97
Amendment [BZ]*	01-OCT-97	02-OCT-97	08-OCT-97
Amendment [BC]*	10-NOV-97	12-NOV-97	18-NOV-97

*Subject of this review.

NAME AND ADDRESS OF APPLICANT:

Bayer Corporation
Pharmaceutical Division
3525 North Regal Street
Spokane, WA 99208

ATTN: David L. Mirabell
Manager
Regulatory Affairs
Tel: (509) 489-5656

DRUG PRODUCT NAME:

Proprietary: — Epinephrine Injection, USP (1:1000)
Nonproprietary/USAN: Epinephrine Injection
Code Name/#:
Chem. Type/Ther. Class: 3S
Established Name of Drug Substance: Epinephrine: 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethanol

PHARMACOL. CATEGORY/INDICATION: Adrenergic

DOSAGE FORM: Injection

STRENGTHS: — (1:1000)

ROUTE OF ADMINISTRATION: Subcutaneous or Intramuscular

Rx/OTC: Prescription

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

Epinephrine, USP. $C_9H_{13}NO_3$. 183.21
[Adrenaline is BAN; Epinephrine Hydrochloride is JAN]
1,2-Benzenediol,(R)- 4-[1-hydroxy-2-(methylamino)ethyl]-1,2-benzenediol. CAS-51-43-4

For structure, see "USP Dictionary of USAN and International Drug Names".

SUPPORTING DOCUMENTS:

DMFs:

DMF Number	Holder	Subject	Status	Date Reviewed	Referenced Section in the NDA
[redacted]	[redacted]	[redacted]	Inadequate	3/14/97	3.2
[redacted]	[redacted]	[redacted]	adequate	3/11/97	3.3

CONSULTS:

1. The new proposed trademark names for the Bayer auto-injector are: [redacted] and TwinJect™. The applicant has chosen [redacted] However, Trademark Consult objected the [redacted] (only TwinJect™ is acceptable).

2. An EER requested on March 14, 1997 for all facilities involved in synthesis, release, and stability testing of drug substance and manufacturing, packaging, in-process testing, release and stability testing of drug products was found not acceptable with the exception of the Bayer facility. (See attached memo dated September 12, 1997)

3. Biometrics consult for the proposed expiration dating period can not be forwarded because the requested stability data are not provided.

4. EA is not necessary per new EA guidance. (See Amendment dated November 10, 1997)

REMARKS/COMMENTS:

1. Methods validation by the Agency will be deferred pending resolution of deficiencies in the methods.

2. Amendment dated 5/29/97 contains information on performance testing of [redacted] at [redacted] time station, cloth/fabric penetration study data, and [redacted] stability data.

3. Although [redacted] stability data for [redacted] alone appear to be all right, the stability protocol *per se* should be modified as we indicated earlier (see Chem. Rev. #1).

4. Amendment dated 9/5/97 is applicant's response to our deficiency letter dated 5/5/97. Applicant states that some of the information requested are not appropriate even though it took more than 4 months for them to come up with such argument.

5. The deficiency items in the Chemistry Review #2 are still outstanding. Therefore review of the labeling amendment dated October 1, 1997 is premature.

CONCLUSION AND RECOMMENDATION:

The deficiencies in the Chemistry Review #2 remain outstanding. This NDA should be considered to be not approvable from CMC standpoint. See Chemistry Review #2.

CK

Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc:
Orig. NDA #20-800
HFD-570 Division File
HFD-570/CKim
HFD-570/GPoochikian
HFD-570/RNicklas
HFD-570/SWilliams
HFD-570/AChen
HFD-570/DToyer
R/D Init. By: CK

doc. NDA 20-800.CR3

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

OCT 7 1997

Division of Pulmonary Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-800 **CHEM. REVIEW #**: 2 **REVIEW DATE**: October 02, 1997

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	05-DEC-96	06-DEC-96	16-DEC-96
Amendment [BZ]	10-JAN-97	13-JAN-97	22-JAN-97
Amendment [BC]	10-JAN-97	13-JAN-97	22-JAN-97
Amendment [BZ]	14-FEB-97	18-FEB-97	25-FEB-97
Amendment [BC]	03-APR-97	09-APR-97	15-APR-97
Amendment [BC]	09-APR-97	10-APR-97	15-APR-97
Amendment [BC] *	29-MAY-97	30-MAY-97	04-MAY-97
Amendment [BC] *	05-SEP-97	08-SEP-97	11-SEP-97

*Subject of this review.

NAME AND ADDRESS OF APPLICANT:

Bayer Corporation
Pharmaceutical Division
3525 North Regal Street
Spokane, WA 99208

ATTN: David L. Mirabell
Manager
Regulatory Affairs
Tel: (509) 489-5656

G PRODUCT NAME:

Proprietary: — Epinephrine Injection, USP (1:1000)
Nonproprietary/USAN: Epinephrine Injection
Code Name/#:
Chem. Type/Ther. Class: 3S
Established Name of Drug Substance: Epinephrine: 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethanol

PHARMACOL. CATEGORY/INDICATION: Adrenergic

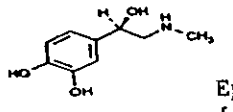
DOSAGE FORM: Injection

STRENGTHS: — (1:1000)

ROUTE OF ADMINISTRATION: Subcutaneous or Intramuscular

Rx/OTC: Prescription

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:



Epinephrine, USP. $C_9H_{13}NO_3$. 183.21
[Adrenaline is BAN; Epinephrine Hydrochloride is JAN]
1,2-Benzenediol, (R)- 4-[1-hydroxy-2-(methylamino)ethyl]-1,2-benzenediol. CAS-51-43-4

SUPPORTING DOCUMENTS:

DMFs:

DMF Number	Holder	Subject	Status	Date Reviewed	Referenced Section in the NDA
			Inadequate	3/14/97	3.2
			adequate	3/11/97	3.3

CONSULTS:

1. The new proposed trademark names for the Bayer auto-injector are: and TwinJect™. Project Manager's Trademark Consult Request (7/16/97) for the proposed names is pending.

2. An EER requested on March 14, 1997 for all facilities involved in synthesis, release and stability testing of drug substance and manufacturing, packaging, in-process testing, release and stability testing of drug products was found not acceptable. (See attached memo dated September 12, 1997)

3. Biometrics consult for the proposed expiration dating period can not be forwarded because the requested stability data are not provided.

4. EA is not necessary per new EA guidance. The applicant will withdraw the EA portion of the submission. (Communication between project manager and applicant)

REMARKS/COMMENTS:

1. Methods validation by the Agency will be deferred pending resolution of deficiencies in the methods.

2. Amendment dated 5/29/97 contains information on performance testing of at time station, cloth/fabric penetration study data, and stability data.

3. Although stability data for alone appear to be all right, the stability protocol *per se* should be modified as we indicated earlier (see Chem. Rev. #1).

4. Amendment dated 9/5/97 is applicant's response to our deficiency letter dated 5/5/97. Applicant states that some of the information requested are not appropriate even though it took more than 4 months for them to come up with such argument.

CONCLUSION AND RECOMMENDATION:

This NDA should be considered to be not approvable from CMC standpoint. See the deficiencies in draft letter.

CK

Chong-Ho Kim, Ph.D.
Review Chemist, HFD-570

cc:
Orig. NDA #20-800
HFD-570 Division File
HFD-570/CKim
HFD-570/GPoochikian
HFD-570/RNicklas
HFD-570/SWilliams
HFD-570/AChen
HFD-570/DToyer
R/D Init. By CK

doc. NDA 20-800.CR2

16 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

OCT 21 1998

Division of Pulmonary Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-800 **CHEM. REVIEW #**: 4 **REVIEW DATE**: October 20, 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	05-DEC-96	06-DEC-96	16-DEC-96
Amendment[BZ]	10-JAN-97	13-JAN-97	22-JAN-97
Amendment[BC]	10-JAN-97	13-JAN-97	22-JAN-97
Amendment[BZ]	14-FEB-97	18-FEB-97	25-FEB-97
Amendment[BC]	03-APR-97	09-APR-97	15-APR-97
Amendment[BC]	09-APR-97	10-APR-97	15-APR-97
Amendment[BC]	29-MAY-97	30-MAY-97	04-JUN-97
Amendment[BC]	05-SEP-97	08-SEP-97	11-SEP-97
Amendment[BZ]	01-OCT-97	02-OCT-97	08-OCT-97
Amendment[BC]	10-NOV-97	12-NOV-97	18-NOV-97
Amendment[AC]*	29-MAY-98	01-JUN-98	09-JUN-98
Amendment[BZ]*	17-JUN-98	19-JUN-98	23-JUN-98
Amendment[BC]*	16-JUL-98	17-JUL-98	22-JUL-98
Amendment[BC]*	24-AUG-98	25-AUG-98	27-AUG-98

*Subject of this review.

NAME AND ADDRESS OF APPLICANT:

Bayer Corporation
Pharmaceutical Division
3525 North Regal Street
Spokane, WA 99208

ATTN: David L. Mirabell
Manager
Regulatory Affairs
Tel:(509) 489-5656

DRUG PRODUCT NAME:

Proprietary: TwinJect™ Epinephrine Injection, USP (1:1000)[Previously —

Nonproprietary/USAN: Epinephrine Injection

Code Name/#:

Chem. Type/Ther. Class: 3S

Established Name of Drug Substance:
Epinephrine: 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethanol

PHARMACOL. CATEGORY/INDICATION: Adrenergic

DOSAGE FORM: Injection

STRENGTHS: — (1:1000)

ROUTE OF ADMINISTRATION: Subcutaneous or Intramuscular

Rx/OTC: Prescription

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

Epinephrine, USP. $C_9H_{13}NO_3$. 183.21
[Adrenaline is BAN; Epinephrine Hydrochloride is JAN]
1,2-Benzenediol,(R)- 4-[1-hydroxy-2-(methylamino)ethyl]-1,2-benzenediol. CAS-51-43-4

SUPPORTING DOCUMENTS:

DMFs:

DMF Number	Holder	Subject	Status	Date Reviewed	Referenced Section in the NDA
[redacted]	[redacted]	[redacted]	not adequate	3/14/97	3.2
[redacted]	[redacted]	[redacted]	adequate	3/11/97	3.3

CONSULTS:

1. CDER Labeling and Nomenclature Committee finds the proposed proprietary name unacceptable; one recommendation is to use "[redacted] instead of "2". (See attached MEMO dated 3/4/97)

2. An EER request(3/14/97) for all facilities involved in synthesis, release and stability testing of drug substance and manufacturing, packaging, in-process testing, release and stability testing of drug products is pending.

3. Biometrics consult for the proposed expiration dating period will be requested shortly.

4. EA review will be done separately.

REMARKS/COMMENTS:

1. Methods validation by the Agency should be deferred pending resolution of deficiencies in the methods as requested.

CONCLUSION AND RECOMMENDATION:

This NDA should be considered to be not approvable from CMC standpoint. See the deficiencies in draft letter.

Chong-Ho Kim, Ph.D. 7/11
Review Chemist, HFD-570

cc:
Orig. NDA #20-800
HFD-570 Division File
HFD-570/CKim
HFD-570/GPoochikian
HFD-570/RNicklas
HFD-570/SWilliams
HFD-570/AChen
HFD-570/DToyer
R/D Init. By: /S/

doc.NDA 20-800.CR1

20 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling