CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-800

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-800 SUPPL # __
Trade Name Twinject Auto-Injector__ Generic Name epinephrine injection 1:1000
Applicant Name Holister-Stier Laboratories, LLC
HFD- 570
Approval Date May 30, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X__/

   If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /___/ NO /_X__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   There was no PK data. The applicant is relying on the Agency's finding of safety and effectiveness for the Epi-Pen NDA and to literature data to support approval.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /_X__/ NO /___/

If yes, NDA # 19-430 Drug Name EpiPen Auto-Injector

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /_X__/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

A clinical trial is not necessary and the sponsor is relying on the Agency's finding of safety and efficacy for the EpiPen NDA and literature data to support approval.

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X__/ NO /_ __/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # None submitted. Referred to NDA 19-430

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the

NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of

the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Ladan Jafari

Signature of Preparer Date 5-30-03

Title: Regulatory Project Manager

Badrul Chowdhury, M.D.

Signature of Office or Division Director Date 5-30-03

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Badrul Chowdhury
5/30/03 04:41:12 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-800	Efficacy Supplement Type SE-	Supplement Number
Drug: Twinject Auto-Injector (epinephrine 1:1000)		Applicant: Hollister-Stier Laboratories, LLC
RPM: Ladan Jafari	HFD-570	Phone #301-827-1084
Application Type: ( ) 505(b)(1) (X) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): Epipen	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	Respiratory
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	July 22, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	(X) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	December 1996

Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NA (December 4, 1997), NA (Nov. 9, 1998), AE (Feb. 17, 2000), NA (Sep. 14, 2000), AE (Dec. 18, 2001), AE (Jan. 29, 2003)
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	May 28, 2003
• Original applicant-proposed labeling	December 5,1996
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	October 29, 2002
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	None
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	January 29, 2003
• Reviews _	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	See attached.
❖ Memoranda and Telecons	See attached.
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	March 6, 1996
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	May 27, 2003
❖ Clinical review(s) *(indicate date for each review)*	January 24, 2003
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	October 18, 2002
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	June 26, 1997
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC information	
❖ CMC review(s) *(indicate date for each review)*	May 28, 2003 (Last review)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	N/A
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: May 21, 2003 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	February 9, 2000
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. *0910-0297*
Expiration Date: *November 30, 1996.*

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Bayer Corporation
Pharmaceutical Division
3525 N. Regal Street
Spokane, WA 99207

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

Contact: Arthur Edwards
Phone: (203) 812-2630

3. TELEPHONE NUMBER *(Include Area Code)*
(509) 489-5656

4. PRODUCT NAME
Epinephrine Injection, USP (1:1000)

DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER
[redacted]3132

7. LICENSE NUMBER/NDA NUMBER
NO20800

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

☒ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES ☒ NO *(See reverse if answered YES)*

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse if answered YES)*

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
David L. Mirabell	Manager, Regulatory Affairs	12-5-96

15 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

10 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

7 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

NDA 20-800
Meeting Date: January 23, 2002

Hollister-Stier Laboratories, LLC Representatives:

Derek Constable, Ph.D., Director, New Product Discovery
Terance Kordash, M.D., Vice President, Scientific & Medical Affairs
David Mirabell, Director, Regulatory Affairs & Professional Services
Shirley Williamson, Director, Quality Assurance

Division of Pulmonary & Allergy Drug Products (DPADP) Representatives:

Badrul Chowdhury, M.D., Medical Team Leader
Ladan Jafari, Regulatory Project Manager
Chong-Ho Kim, Ph.D., Chemistry Reviewer
Richard Nicklas, M.D., Clinical Reviewer
Guirag Poochikian, Ph.D., Chemistry Team Leader
Stephen Langille, Ph.D., Microbiology Reviewer

Background: The Division issued an approvable letter for Hollister-Stier's new drug application (Twinject) on December 2001. Upon receipt of this action letter, HollisterStier submitted a request dated December 19, 2001, to meet with the Division to discuss several deficiencies of the approvable letter. Hollister-Stier submitted a briefing package on January 3, 2002, which outlined responses to several of the deficiencies listed in the approvable letter and asked if the Division found those responses acceptable. Hollister-Stier also included a copy of their revised labeling and asked if the Division could further comment on the revised labeling.

CMC:

Question 1.a.: The Division indicated that since the new proposal is more reflective of the data, the proposal is acceptable.

Question 1.b.: The Division indicated that we will comment after a complete response to the action letter is submitted.

Question 1.c.: The Division found the response acceptable, and indicated that based on the actual data, the mean ±SD is 1.43 to 1.59 mg/mL.

Question 1.d.: The Division referred to comment 1.a. above and indicated that the proposal is acceptable.

Question 1.e.: The Division did not find the proposal for fill volume acceptable and indicated that since the target fill volume is [redacted] the upper limit can be set as target [redacted] Hollister-Stier agreed to inform Abbott Laboratories to revise the fill volume.

Question 1.f.: The Division indicated that we will comment after a complete response to the action letter is submitted.

NDA 20-800
Meeting Date: January 23, 2002

Question 2.a.and 2.b.: The Division indicated that we will comment after a complete response to the approvable letter is submitted.

Question 3.a.: The Division did not find the proposal acceptable and indicated that Hollister-Stier must test for [redacted] for the first year, perform identification test [redacted] for the first year, establish specifications for chlorobutanol and test [redacted] s for the first year, and test the sterility of the product at time 0 as well. The Division also indicated that due to the limited data, acceptance criteria for total known impurities, total unknown impurities, and total impurities are not justified. The Division stated since the [redacted] n no longer part of this application, the data from [redacted] s no longer acceptable, and that the data should be generated from the new [redacted] system. The Division discussed the degradation products and indicated that in order to set expiry, Hollister–Stier must provide lower levels of degradation products. The Division indicated that the expiry could be extended by means of a prior approval supplement, if additional data is provided.

Question 3.b.: The Division indicated that we will comment after a complete response to the approvable letter is submitted.

Question 3.c.: The Division did not find the proposal acceptable and indicated that because a preservative is used in this drug product, the preservative effectiveness must be demonstrated. The Division asked that the preservative effectiveness be demonstrated outside the proposed extremes.

Question 3.d.: The shelf-life specification limit (NMT [redacted] for [redacted] total known impurities, total unknown impurities, must be based on the available stability data. Also see comment 3.a. above.

Question 3.e.: The Division indicated that we will comment after a complete response to the approvable letter is submitted.

Question 4.a. and 4.b.: The Division found the responses acceptable.

Question 5: The Division indicated that we will comment after a complete response to the approvable letter is submitted. However, the Division stated that Hollister-Stier must perform verification studies of [redacted] data and reports. Hollister must include the acceptance criterion and test method for extractables in the incoming raw material specifications and test methods. Hollister-Stier must also include the results on the Certificate of Analysis.

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Meeting Date: January 23, 2002

Question 6.a. and 6.a.(1): The Division did not find the response acceptable and stated that Hollister-Stier must place the [redacted] of Twinject on stability study. The stability study should be performed at 25°C/60%RH and 40°C/75%RH. The Division emphasized that this data must be provided for both Twinject as well as the [redacted] system. Hollister-Stier indicated that they have provided the [redacted] stability data on both 25°C and 40°C. The Division indicated that Hollister-Stier must verify in their complete response to the application, that the data submitted was for both Twinject and the [redacted] system, and that it was from the production scale batches of the commercial batches.

Question 6.a.(2): The Division did not find the response acceptable and indicated that Hollister-Stier must indicate with data where the loss of chlorobutanol is originating from If chlorobutanol is not degrading, or if it is being reduced during manufacturing due to being very volatile.

Question 6.a.(3): The Division did not find the response acceptable. The Division indicated that the sterility test be performed at time 0 and at expiry. In addition, Hollister-Stier should submit sterility data at the last test interval in the forthcoming amendment (e.g., 12-month).

Question 6.a.(4): The Division indicated that we will comment after a complete response to the action letter is submitted. The Division also informed Hollister-Stier that the performance test attributes on table 5B were not listed on the stability protocol (table 5C).

Question 6.b.: The Division did not find the response acceptable and indicated that Hollister-Stier must propose an acceptable limit for chlorobutanol. Additional comments will be provided after the submission of the complete response.

Question 6.c:

(1) The Division did not find the proposal acceptable and indicated that the increase in [redacted] within [redacted] may be due to an inadequate test method, and asked that Hollister-Stier develop a stability indicating test method.

(2) The Division stated that the dramatic reduction in the initial chlorobutanol level may be an indication of inadequate manufacturing parameter or inadequate method. These should be re-examined. The Division suggested that perhaps the titration method could be improved.

(3) Moreover, the increase in chlorobutanol level observed in [redacted] have not been explained (refer to 6.c (3) above), and maybe due to an inadequate method. Develop a stability test method, and note that your claim that the observed data are due to the inter-assay variations of the method is not acceptable.

Question 8.a.: The Division reminded Hollister-Stier that they should inform the contract manufacturer to get concurrence from both Hollister-Stier and the Agency prior to changing any procedures.

Question 8.b: The Division did not find the response acceptable and indicated that endotoxin testing is required at expiry because of the possibility of [redacted] over time. The Division indicated that Hollister-Stier must include the levels of endotoxin in the complete response and demonstrate the sensitivity of the assay.

Labeling: The Division indicated that we have not reviewed the labeling in detail, however, upon cursory review, we have the following comments.

- The change in storage condition to [redacted] is not acceptable. The Division requested that the storage condition be set at 20-25°C.
- The Division asked that the [redacted] section be removed from the labeling.
- The Division asked that Hollister-Stier include a clear statement throughout the labeling which instructs the patients to [redacted]

Additional comments: The Division informed Hollister-Stier that from a public health point of view, it is important to get this product on the market and indicated that because this is a life saving product, the Division would like to work with Hollister-Steir to get an approval as soon as possible and after all the deficiencies are resolved.

Ladan Jafari, Regulatory Project Manager

NDA 20-800
Meeting Date: January 23, 2002

Initialed by: Kim/2-8-02
Poochikian/2-11-02
Nicklas/2-8-02
Chowdhury/2-8-02, 2-19-02

Filename: Hollister mtgmin.doc

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

/s/

Ladan Jafari
2/20/02 02:20:02 PM

INDUSTRY MEETING MINUTES

DATE:	November 16, 1998
TIME:	10:30 a.m. to 11:30 a.m.
PLACE:	Parklawn Conference Room "Q"
MEETING TYPE:	Chemistry Guidance
APPLICANT:	Bayer Pharmaceutical
NDA:	20-800
DRUG:	Epinephrine 1:1000
IMTS #:	**3498**

DIVISION OF PULMONARY DRUG PRODUCTS

Mr. Keary Dunn	Project Manager
Dr. Peter Honig	Clinical Team Leader
Dr. John K. Jenkins	Division Director
Dr. Chong-Ho Kim	Chemistry Reviewer
Dr. Richard Nicklas	Clinical Reviewer
Dr. Guirag Poochikian	Chemistry Team Leader
Dr. Joseph Sun	Pharmacology and Toxicology Team Leader
Dr. Denise Toyer	Project Manager

BAYER PHARMACEUTICALS, INC.

Dr. Derek W. Constable	Director, Research and Development
Dr. Richard D. Costa	Director, Quality Assurance
Mr. David L. Mirabell	Manager, Regulatory Affairs

Background

Bayer Pharmaceutical Division has submitted a new drug application (NDA) which uses a marketed product (i.e. [redacted] epinephrine 1:1000 [redacted] as the main constituent of the [redacted] device. [redacted] has provided manufacturing information to Bayer for this application. Unfortunately, [redacted] was unable to attend this meeting and Bayer will provide [redacted] comments on the deficiencies discussed.

On November 9, 1998, the Division issued a "Not Approvable" letter to Bayer Pharmaceuticals for this new drug application. The objective of this meeting is to further clarify the deficiencies which were listed in the November 9, 1998, letter. The deficiencies are listed below in bold.

1. **The following comments pertain to test methods and acceptance criteria for impurities and degradation products.**

   a. **In response to our request to provide specifications and test methods for impurities/degradation products (individual and total), it was stated that the [redacted] April 3, 1997, amendment). A reminder of your commitment to submit these data for review was included in our December 4, 1997, letter. However, the requested information which has not yet been adequately addressed and should be submitted in detail for review.**

   Clarification: The Division indicated that deficiency 1(a) is an introduction to deficiencies 1(b) through 1(e).

   b. **Although a report [redacted] from the [redacted] describes the method to detect and quantitate epinephrine and associated degradation products, the method is not acceptable; [redacted] should also be specified as a degradation product.**

   Clarification: Bayer indicated that [redacted] has additional data that show that [redacted] does not form during the manufacturing process. These data need to be provided to the Division [redacted] has a secondary method that will augment the premise that they cannot detect formation of [redacted] Bayer noted that [redacted] indicated that the peak doesn't reach the [redacted] level so they do not feel that they have to qualify this degradation product. The Division reiterated the fact that despite the use of USP testing for drug products the Division must ensure that the drug is safe and effective. Therefore, USP testing may not be sufficient and additional testing may be required.

   c. **Specifications for known impurities, unknown impurities (individual and total), and total impurities should be provided. The proposed acceptance criteria should be justified with stability data.**

   Clarification: [redacted] informed Bayer that they are currently developing and instituting a new manufacturing method which will be used throughout the epinephrine 1:1000 [redacted] product line. [redacted] is willing to provide these data on an ongoing basis while the GTR process is being implemented. However, they do not want to institute any specifications using this ongoing process at the current time. The Division recommended that [redacted] submit data (using the old process) for drug product on expiry, chromatograms, and analysis, for reserve samples or batches on stability. Once these data have been reviewed, the Division will discuss specifications. Bayer indicated that [redacted] is reluctant to commit to any changes to the manufacturing process which will jeopardize [redacted] market share.

d. **Chemical characterization as well as pharmacological/toxicological information on the — rubber extractables (——— in the chromatogram of an aged sample) should be provided (May 29, 1998, amendment, response 2).**

Clarification: Bayer indicated that the rubber used in the — assembly meets the USP standard for toxicity. ——— currently conducts the USP (i.e., Chapter 87/88) toxicity testing on the total rubber component and they feel that these tests will provide the required extractable information. However, these data have not been provided to the Division. These data should be provided in Bayer's response and the Division will determine if the USP testing is sufficient.

e. **A — test and acceptance criteria should be provided. Standard Operating Procedure — should also be provided for evaluation (May 29, 1998, amendment, response 7).**

Clarification: Bayer noted that ——— has a developed a procedure for a — test (i.e., similar to and acceptance criteria. These data will be submitted in the response once ——— has obtained real-time data using the new method.

f. **Provide the requested information on the immediate container and closure system ——— epinephrine) with regard to composition and appropriate specifications and test methods (May 29, 1998, amendment, response 4 and also refer to comment 1 above).**

Clarification: The Division indicated that code numbers were provided for the composition of the immediate container and closure system. The actual composition should be provided. This information may be provided through a letter of authorization to a DMF. The Division will accept certificates of analysis but the burden is on the applicant to routinely verify that changes are not occurring.

3. **The following additional comments pertain to product specifications (June 17, 1998, amendment, pages 190-192).**

a. **Define the target pH of ——— epinephrine. The proposed acceptance criteria should be justified with stability data.**

Clarification: If there is a pH adjustment then it should be clearly stated in the manufacturing procedure. However if there is no pH adjustment, the SOP should provide a reasonable pH range for release based on historical data to ensure batch to batch reproducibility. Releasing products at pH ——— does not provide the needed assurance unless stability data are generated to demonstrate that products manufactured at both extremes are equally stable.

b. **The proposed breakloose force of [redacted] is wide and should be reduced. Provide data to justify the new proposed specification.**

Clarification: Bayer indicated that [redacted] is reluctant to tighten this specification. Bayer noted that their device will perform at both ranges. The Division requested data to justify that the device will perform at the [redacted] ranges.

c. **The second identification test method and acceptance criteria should be provided.**

Clarification: Bayer should use an additional test method. A chromatographic assay (e.g., HPLC) is acceptable.

d. **The total length of the [redacted] is limited to NLT [redacted] The upper limit should also be provided.**

Clarification: Bayer will provide an upper limit for the [redacted] However, the performance of the device is only dependent upon a minimum [redacted] length which facilitates removal of the needle cover.

e. **The acceptance criteria for the distance between the [redacted] and the top of the [redacted] is limited to NLT [redacted] inches. The upper limit should also be provided.**

Clarification: Bayer will provide a lower limit. However, as mentioned in 3(d) the performance of the device is only dependent upon a minimum length of the [redacted]

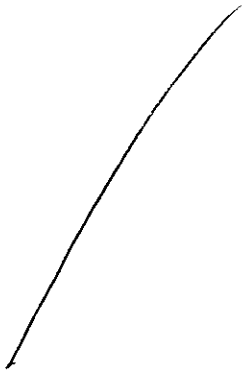
f. **Specifications for volume of dose-1, time to deliver dose-1, and volume of dose-2 should be provided.**

Clarification: Bayer will provide this information. Bayer will provide a target volume with a range. Dose uniformity will be applied to the individual devices in addition to applying an average to the batches.

g. **Table 1 (July 16, 1998, amendment) indicates that the mean for the firing force is [redacted] Therefore the specification should be significantly tightened to reflect the data, e.g., 2.5 - 5.6 pounds (May 29, 1998, amendment, response 3).**

Clarification: Bayer feels they have improved the performance of the device by increasing the size of the [redacted] The range for the firing force is currently [redacted] The Division is concerned about spontaneous firing of the device. Bayer, however, does not want to tighten the specifications but would like to provide a

commitment that they would monitor internal process controls to ensure that the range stays in the median. The Division feels the specifications should be tighter at the beginning of the process. Bayer may request looser specifications once data have been generated to substantiate less stringent specifications. Bayer plans to submit data justifying their position, however the Division strongly recommends that Bayer tighten the range for the firing force.



5. **The following comments pertain to the stability protocol (May 29, 1998, amendment, attachment 4).**

   a. **Dosage Check for the first and second dose has a limit NLT — NMT — This is not acceptable. Modify the limit to reflect actual stability data.**

   b. **The required firing force should be tightened (see comment 3(g) above).**

   c. **The three-points stability protocol should be stated in the revised stability protocol.**

Clarification: Bayer agreed to modify the revised stability protocol to reflect changes made since the first stability protocol was submitted. Additionally, they will review the actual stability data and adjust the dosage check for the first and second dose.

Conclusion

The meeting scheduled for December 15, 1998, will be cancelled. Bayer will review the information provided during this meeting and prepare a response to the not approvable letter. If Bayer has any additional questions or requires additional clarification they will contact the Division for further guidance. The Division strongly reiterated our goal of working with Bayer to ensure that this device is safe and effective and to help facilitate marketing approval.

/S/

Denise P. Toyer, R.Ph., Pharm.D.
Project Manager

cc:
HFD-570/Original NDA
HFD-570/Division File
HFD-570Chen
HFD-570/Dunn
HFD-570/Honig/11-17-98/sent via e-mail/no additional comments received
HFD-570/Jenkins/11-17-98/sent via e-mail/no additional comments received
HFD-570/Kim/11-24-98
HFD-570/Nicklas/11-17-98/sent via e-mail/no additional comments received
HFD-570/Poochikian/12-16-98
HFD-570/Sun/11-17-98/sent via e-mail/no additional comments received
HFD-570/Toyer
HFD-570/Uppoorr

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Toyer

MEMORANDUM

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

DATE: December 20, 1996

FROM: Denise P. Toyer DPT
Project Manager

SUBJECT: NDA 20-800

TO: File

As the new project manager for this NDA, I conducted an administrative review of previous submissions for this NDA. The highlights are listed below.

1. A request for a pre-NDA meeting was submitted on January 18, 1996 by the sponsor. The purpose of this request was to review performance tests and packaging concepts for the Epinephrine Autoinjector (now the Anaguard 2 device).

2. Internal meetings held March 1 and 4, 1996 determined that the Biopharmaceutics and Pharmacology disciplines were not needed at the pre-NDA meeting. Additionally, it was revealed that the sponsor would be using a product (epinephrine _____ which was not approved but had been "grandfathered." At the March 4, 1996 meeting Dr. Yuan Yuan Chiu and the division decided that CMC information would be required for all new NDA's submitted, including those that had originally been "grandfathered." The information required for "grandfathered" products may not be as stringent or detailed as usually required for an NDA but some data must be submitted. The sponsor told Mr. Koung Lee on March 4, 1996 that Bayer did not plan to submit "much data."

3. An industry meeting was held on March 6, 1996. The following is a summary of the recommendations and conclusions from that meeting.

   a. Bayer will pursue the 505(b)(2) pathway for the submission of the NDA.

   b. Complete CMC information and data should be included in

the submission (LOA's to approved NDA's and DMF's).

c. The following suggestions were made to improve the performance testing:

(1) determine the time it takes for normal volunteers to prepare the 2nd injection;

(2) consider color blindness when preparing the protocol since green and red are common colors that color blind patients can't see;

(3) consider testing through clothing;

(4) consider mishandling conditions; and

(5) consider a mechanical stability study.

4. Bayer will submit their final protocol for performance testing.

5. Stability information and stability protocols will be provided.

6. The agency will inform Bayer of the minimum labeling requirements for the auto-injection carrying case within 2 weeks.

Attached are copies of the meeting request, and the minutes for both the internal and industry meeting.

ATTACHMENTS 1) 6 (5

cc: NDA #20-800
HFD-570/Division File
HFD-570/Toyer

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MEETING MINUTES MARCH 6, 1996

PRE-NDA MEETING WITH BAYER PHARMACEUTICALS INC.

DRUG PRODUCT: Epinephrine Auto-injector

ATTENDEES

FDA : John Jenkins, Martin Himmel, Guirag Poochikian, Peter Honig, Chong-Ho Kim, Richard Nicklas, Parinda Jani, Koung Lee, and Brad Gillespie

Bayer: Derek Constable, Nancy Motola, David Mirabell, and [redacted]

Please refer to the sponsor's January 18, 1996 Meeting Request Package for background information and the March 1 and 4, 1996 Internal Meeting Minutes.

Mr. David Mirabell of Bayer stated that they intend to pursue the 505(b)(2) pathway for the submission of the NDA.

Mr. Mirabell said Bayer has had a working relationship with [redacted] since the late 1960's. For the CMC part for the drug substance, Mr. Mirabell said that they could provide the manufacturing profile, certificate of analysis using USP criteria, stability information, and identity testing. He noted that Bayer conducts periodic auditing of their facility for their own assurance.

Mr. Mirabell said that the Ana-Kit, which provides two doses and is marketed without an approved NDA, uses the same epinephrine [redacted] as the one proposed for the auto-injector.

[redacted] of [redacted] noted that the [redacted] which drives the needle produces approximately [redacted] of force.

Dr. Chong-Ho Kim of the Agency asked who manufactured the [redacted] and [redacted] said that [redacted] did.

Dr. John Jenkins, Director of DPDP, asked about the [redacted] in the [redacted] and [redacted] said that the [redacted] issue would be handled in the labeling. Dr. Jenkins asked whether they had performed any tests to determine the time it takes to prepare the second dose. Mr. Mirabell said that the only test that was performed were by their staff and that the labeling would instruct the patients to prepare the second dose soon after administering the first dose. Dr. Jenkins recommended that they might want to consider using volunteers who do not know about their product to use it and see how long it take them to administer the second dose. Dr. Jenkins added that this study could be used for labeling purposes.

Dr. Derek Constable of Bayer gave an overview of their performance criteria which included testing removal of safety cap and sheath, premature firing under normal conditions, force needed from the patient to insure penetration through clothing and skin, no firing, assuring correct volume delivery, preparing 2nd dose, etc. Dr. Chong-Ho Kim of the Agency asked about the dispensing time and Bayer replied that the patient is asked to count to three to assure that the drug is delivered. Dr. Kim asked about testing through clothing and Mr. Mirabell stated that the EpiPen labeling does not say anything about clothing. Dr. Kim asked what they meant by "suitable receptacle" and [redacted] eplied that they have not finalized it yet but they were looking into [redacted]

Dr. Poochikian asked whether the needle would be pushed back into the [redacted] if it were to be pushed through clothing such as jeans. [redacted] said that that couldn't happen.

Dr. Poochikian asked if they had stability data on the device to assure that the device would work after being stored in various conditions such as in the car or pockets. [redacted] said that none of the components of the device would corrode but they will consider conducting some stability studies on the device. [redacted] asked what types of mechanical stability testing would the Division find acceptable. Dr. Poochikian said that they might want to consider [redacted] esting under high humidity and observe the performance characteristics. Dr. Poochikian said that we would not request a [redacted] stability study.

Dr. Kim asked whether Bayer had any cross reference to the [redacted] epinephrine [redacted] Dr. Poochikian added that, technically, a NDA would require a complete CMC section. Some of this information Dr. Poochikian said, could be obtained by getting cross reference from [redacted] or from a DMF. Dr. Constable said that they would have to approach [redacted] Dr. Poochikian asked what if [redacted] changed something? Mr. Mirabell replied that they have had a long relationship with [redacted] and expects that they would be notified if changes were made. Dr. Poochikian said that any change should be formally submitted to the NDA.

Dr. Constable said that the active substance came from [redacted] Dr. Jenkins noted that if the epinephrine [redacted] was an approved NDA, there wouldn't be any problems but since the [redacted].s not marketed under a NDA, there is a need to meet the requirements for a New Drug. Dr. Poochikian said that what they are proposing to submit are mainly anecdotal and would not be adequate but assured them that we would not ask for details that we normally request for new NDA's. Dr. Poochikian said that they will most likely need [redacted] cooperation.

Mr. Mirabell presented two versions of the patient's package insert (PPI) which were wrapped around the cylinder of the auto-injector. One of them was a [redacted] design and the other was a [redacted] design. It was agreed by both parties that the [redacted] design is more desirable since it would give the patient an opportunity to explore the device, learn how it works and allow them to re-wrap the PPI back on the cylinder of the auto-injector.

Dr. Poochikian asked whether the [redacted], which covers the needle portion of the auto injector, could be placed back on the auto-injector after the first injection. [redacted] replied that it could not because of the lack of clearance created from the protrusion of the needle after the first dose is administered.

Dr. Poochikian said that the auto-injector carrying case will need proper labeling. Mr. Mirabell said that the size of the carrying case will be reduced but they will need adequate time to print the required labeling because of the composition of the carrying case. Dr. Jenkins said that we will get this information to them within a week or two regarding what would be required.

Dr. Poochikian asked when they planned on submitting the NDA and they said June or July.

Dr. Jenkins asked what their plans were for the Ana-Kit if this product was to be approved and they said that they would continue to market both products but believe that the auto-injector would cannibalize the sale of the Ana-Kit.

Dr. Poochikian noted that it appears that the rate limiting step is the CMC. Dr. Constable assured us that they will have further discussion with [redacted]

OUTCOMES OF THE MEETING

1. Bayer will pursue the 505(b)(2) pathway for the submission of the NDA.

2. Complete CMC information and data should be included in the submission. Appropriate and authorized cross references to approved NDA's and DMF's may be used.

3. The following suggestions were made to improve the performance testing:

   a. Determine the time it takes for normal volunteers to prepare the 2nd injection;

   b. consider color blindness when preparing the protocol since green and red are common colors that color blind patients can't see;

c. consider testing through clothing;

d. consider mishandling conditions; and

e. consider a mechanical stability study.

4. Bayer will submit their final protocol for performance testing.

5. Stability information and stability protocol will be provided.

6. The Agency will inform Bayer the minimum labeling requirements for the auto-injector carrying case within 2 weeks.

LS

Koung Lee, Project Manager

cc: Pulmonary Files
HFD-570/C.Schumaker
HFD-570/J.Jenkins/3-26-96
HFD-570/M.Himmel/3-25-96
HFD-570/P.Honig/3-22-96
HFD-570/G.Poochikian/3-21-96
HFD-570/D.Nicklas/3-21-96
HFD-570/C.Kim/3-20-96
HFD-570/P.Jani
HFD-870/B.Gillespie
HFD-570/K.Lee/3-8-96

MEETING MINUTES

Acting Director Review

NDA: 20,800
Product: TwinJect (epinephrine injection)
Indication: emergency treatment of severe allergic reactions
Date: 1/29/03
Reviewer: Marianne Mann, Acting Director, DPADP

This review summarizes relevant issues in NDA 20,800 for TwinJect epinephrine Injection. There have been multiple NDA submissions for this product back to December 5, 1996.

Overview:
This NDA package contains clinical, biopharmacology, microbiology, pharmacology/toxicology, and chemistry reviews. This NDA is considered acceptable from all disciplinary respects, however the manufacturing inspection performed in the field led to a withhold recommendation. The withhold recommendation is based on a review of the FDA-483 issues by the local office (SEA-DO) to the sponsor regarding the Hollister-Stier's facility. Consequently, this NDA will receive an approvable action.

Marianne Mann, Acting Director, DPADP

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/s/

Marianne Mann
1/29/03 12:57:35 PM
MEDICAL OFFICER

Acting Director Review

NDA: 20,800
Product: TwinJect (epinephrine injection)
Indication: emergency treatment of severe allergic reactions
Date: 12/14/01
Reviewer: Marianne Mann, Acting Director, DPADP

This review summarizes relevant issues in NDA 20,800 for TwinJect epinephrine Injection. The proposed name "TwinJect" has been reviewed and is acceptable.

Overview:
This NDA package contains clinical, biopharmacology, microbiology, pharmacology/toxicology, and chemistry reviews. Issues within each discipline are outlined below. This is one of multiple NDA submissions dating back to 12/5/96 for this particular product. An approvable letter was sent to the sponsor most recently on 2/17/00, with the issues being chemistry concerns, and labeling changes.

Clinical:
There are no clinical data provided for this injection system since epinephrine is well defined as effective for the treatment of life-threatening allergic reactions. The clinical review therefore mainly emphasized labeling, which was extensively rewritten by the clinical review team. One major concern expressed in the 2/17/00 approvable letter was that the sponsor should perform clinical use studies in patients with disabilities such as arthritis to see is such patients could perform the steps necessary for administering a potentially needed second dose of epinephrine. The sponsor has not performed such studies, and has rather chosen labeling stating that the TwinJect product is not appropriate for such a population. The Division agrees with this labeling, and will not require clinical studies in this population. Many labeling changes have been submitted by the clinical review team, who recommend an approvable action based on labeling.

Chemistry:
The chemistry review history of this product is complicated in that in earlier submissions the supplier of epinephrine was [redacted], while the current supplier of epinephrine is Abbott Laboratories. Chemistry deficiencies remain in this application, but they should be able to be addressed in a reasonable timeframe by the sponsor.

Biopharmacology:
There are no new biopharmacology data submitted in this submission. The most recent biopharmacology review is dated 6/26/97, which entailed a review of literature articles that described the pharmacokinetics of epinephrine. No major issues were raised in this review.

Microbiology:

A 9/28/01 Microbiology review outlined two deficiencies. The sterilization process for the needles that are applied to the end of the cartridges required needed to be clearly defined so that sterility could be assured. Endotoxin testing was recommended as part of the routine stability testing, and, at a minimum, should take place at expiry.

Pharmacology/Toxicology:
A pharmacology/toxicology review dated August 2, 2000 is included in this package. No concerns were raised in this review.

Conclusions:
An approvable action on this NDA supplement will be taken. A letter listing outstanding chemistry deficiencies and two microbiology concerns will be sent to the sponsor, along with recommended labeling.

LS

Marianne Marn, Acting Director, DPADP

Addendum to Acting Director Review

NDA: 20,800
Product: TwinJect (epinephrine injection)
Indication: emergency treatment of severe allergic reactions
Date: 12/14/01
Reviewer: Marianne Mann, Acting Director, DPADP

This addendum clarifies an error in the original Acting Director addendum to this Review, also dated 12/14/01. The original review states:

The chemistry review history of this product is complicated in that in earlier submissions the supplier of epinephrine was [redacted] while the current supplier of epinephrine is Abbott Laboratories.

The review should instead state:

The chemistry review history of this product is complicated in that for earlier submissions the supplier of the [redacted] for delivering epinephrine was [redacted] while the current supplier for the [redacted] is Abbott Laboratories.

Marianne Mann, M.D.
Acting Director, DPADP

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/s/

Marianne Mann
12/14/01 12:46:38 PM
MEDICAL OFFICER

MEDICAL TEAM LEADER MEMORANDUM

DATE:	May 27, 2003
TO:	NDA 20-800
FROM:	Eugene J. Sullivan, MD, FCCP Acting Medical Team Leader, DPADP
THROUGH:	Badrul Chowdhury, MD, PhD Director, DPADP
SUBJECT:	Medical Team Leader review of Twinject™ Auto-Injector Epinephrine Injection USP 1:1000; Submission dated May 22, 2003

Administrative/Overview

NDA 20-800 was submitted by Bayer Corporation on December 5, 1996, at which time the proposed trade name was — . In 1999, ownership of the NDA was transferred to Hollister-Stier Laboratories LLC. The drug product is a patient-actuated injector device that contains 1.1mL of epinephrine injection, USP, (1:1000 or 1mg/mL). The product can deliver up to two individual subcutaneous or intramuscular doses of 0.3mL (0.3mg of epinephrine) (the remaining 0.5mL left in the device cannot be further administered). The first dose is administered automatically after the patient prepares the device for firing. The second dose is administered manually, after partial disassembly of the device. The proposed indication is the emergency treatment of severe allergic reactions (Type 1) including anaphylaxis, [redacted].

This is one of multiple cycles of this NDA submission. From the clinical perspective, the application has been considered adequate for approval since the original submission. However, a number of CMC issues have previously precluded approval. The most recent action was an Approvable action, which was taken on January 29, 2003. At that time all of the CMC issues had been adequately addressed, with the exception of the Establishment Evaluation Review (EER), which had not yet been performed. For further details, the reader is referred to the Medical Team Leader Memorandum regarding the submission dated July 26, 2002.

The EER has now been completed and was acceptable. Therefore, the application is now acceptable for Approval from all disciplines. In preparation for approval, a final review of the product label was performed.

Labeling Issues

A final labeling review was performed, and the following changes to the proposed label will be requested. [These comments refer to the version of the product label submitted on January 29, 2003.]

1. Page 2, WARNINGS section: The last sentence of the first paragraph should read: "If there is an accidental injection into these areas, advise the patient to inform the healthcare provider of the accidental injection when he/she goes to the nearest emergency room for further treatment of anaphylaxis."

2. Page 2, PRECAUTIONS section: The sentence that begins on page 2 and continues on page 3 should read: " Patients with diabetes may develop increased blood glucose levels following epinephrine administration."
3. Page 3, OVERDOSAGE section: The last sentence of the first paragraph should read: "If prolonged hypotension follows such measures, it may be necessary to administer another pressor drug."
4. Page 3, OVERDOSAGE section: The third paragraph should read: "If an epinephrine overdose induces pulmonary edema that interferes with respiration, treatment consists of a rapidly acting alpha-adrenergic blocking drug, and/or respiratory support."
5. Page 4, DOSAGE AND ADMINISTRATION SECTION: The second paragraph should be replaced with the following two paragraphs:
"Twinject™ is capable of delivering two doses of 0.3mg (0.3mL of 1:1000 dilution of epinephrine) each. The first dose is available for autoinjection by the patient, and the second dose is available for manual injection by the patient following a partial disassembly of the Twinject™ device.

Twinject™ is intended for use by adults and children who weigh 30 kilograms (approximately 66 pounds) or greater. The usual dose of epinephrine for allergic emergencies in patients who weigh 30 kilograms or greater is 0.3mg (0.3mL of 1:1000 dilution of epinephrine). A dosage of 0.01 mg/kg body weight is usually recommended for pediatric patients. Since the dose of epinephrine delivered from Twinject™ is fixed at 0.3mg, the physician should consider other forms of injectable epinephrine if doses lower than 0.3mg are felt to be necessary (e.g. children less than 30 kilograms). The prescribing physician should carefully assess each patient to determine the most appropriate dose of epinephrine, recognizing the life-threatening nature of the reactions for which this drug is being prescribed."

Recommendation

The recommendation is for Approval of this application, with the above labeling changes.

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/s/

Eugene Sullivan
5/27/03 03:20:59 PM
MEDICAL OFFICER

Badrul Chowdhury
5/27/03 03:51:42 PM
MEDICAL OFFICER

MEDICAL TEAM LEADER MEMORANDUM

DATE:	January 14, 2003
APPLICATION:	NDA 20-800
FROM:	Eugene J. Sullivan, MD, FCCP Acting Medical Team Leader, DPADP
SUBJECT:	Secondary medical review of Twinject™ Auto-Injector Epinephrine Injection USP 1:1000; Submission dated July 26, 2002
CC:	HFD-570: Chowdhury, Nicklas, Jafari

Administrative/Overview

NDA 20-800 was submitted by Bayer Corporation on December 5, 1996, at which time the proposed trade name was [redacted] In 1999, ownership of the NDA was transferred to Hollister-Stier Laboratories LLC. The drug product is a patient-actuated injector device that contains 1.1mL of epinephrine injection, USP, (1:1000 or 1mg/mL). The product can deliver up to two individual subcutaneous or intramuscular doses of 0.3mL (0.3mg of epinephrine) (the remaining 0.5mL left in the device cannot be further administered). The first dose is administered automatically after the patient prepares the device for firing. The second dose is administered manually, after partial disassembly of the device. The proposed indication is the emergency treatment of severe allergic reactions (Type 1) including anaphylaxis, [redacted]

This is one of multiple cycles of this NDA submission. The most recent action was an Approvable action on December 18, 2001. The current submission is a response to the December, 2001 action. At the time of the original submission in 1996, the clinical component of the application was deemed acceptable to allow approval. The primary issues that have precluded approval over the years have been CMC-related.

Self-injectable epinephrine is a very important treatment of severe, life-threatening allergic reactions. Currently there is only one marketed self-injectable epinephrine product. Therefore, this product would represent an important addition to the market.

Chemistry and Manufacturing

Twinject™ Auto-Injector Epinephrine Injection USP 1:1000 consists of an automatic needle insertion/injection device that contains a [redacted] containing 1.1mL of epinephrine injection, USP, 1:1000. The epinephrine drug substance is manufactured by [redacted] The original supplier of the [redacted] for delivering epinephrine was [redacted] The current supplier is Abbott Laboratories.

The major issues precluding approval of this NDA have been CMC-related. The reader is referred to the separate CMC Review for details regarding the specific deficiencies. The CMC review team has determined that these deficiencies have been addressed adequately to allow approval, pending a satisfactory EER. The CMC Review also outlines Phase 4 agreements that have been reached with the Applicant. These agreements relate to establishing acceptance criteria for [redacted] and performing

, testing as part of the commercial product stability program until such time as the — specifications have been set.

Pharmacology and Biopharmaceutics
The pharmacokinetics section of the initial NDA submission consisted of published references and a brief review. No new data was included in this submission.

Microbiology
The AE letter of December, 2001 included two microbiology deficiencies. The Applicant was asked to clarify the sterilization process for the needles, and to perform endotoxin testing as part of the routine stability testing, and, at a minimum, at expiry. These issues have been adequately addressed, and the Microbiology Reviewer has recommended Approval (Microbiology Review dated October 7, 2002, Dr. Riley).

Clinical Studies
As agreed upon with the Agency at a pre-NDA meeting held in 1996, the clinical section of the initial NDA submission consisted of published references addressing the pharmacokinetics, pharmacodynamics, toxicology, and clinical efficacy of epinephrine in the treatment of anaphylaxis, as well as a brief review of these articles. This information was supported by a non-invasive study of the time required to administer the second of the two doses contained in the drug product. The Division had previously requested that the Applicant perform a study to examine the time necessary for patients with disabilities (e.g. arthritis) to prepare the second dose of epinephrine. The Applicant chose instead to add language to the label stating that the product is not suitable for patients with such disabilities.

The Division has previously determined that the clinical aspects of the application are sufficient to merit approval. This determination was based on the accepted efficacy of epinephrine in the treatment of life-threatening allergic reactions, the demonstration that the device will deliver the drug product as labeled, and the acceptable safety of epinephrine when used in life-threatening circumstances. The current submission does not contain new clinical information.

Labeling Issues
During previous review cycles the Division has undertaken extensive labeling review, and has communicated revised labeling language to the Applicant. The proposed label contained in the current submission reflects the Division's prior input, and no further labeling changes are necessary. During the current review cycle a consultation from the Division of Surveillance, Research, and Communication Support regarding the product label was obtained.

Recommendation
From the clinical perspective, the application has been considered adequate for approval since the original submission. No new data have been introduced that would alter that decision. According to the CMC review team, the CMC issues, which have long

precluded approval, have now been adequately addressed (pending a satisfactory EER). Therefore, the recommendation is for Approval.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Eugene Sullivan
1/17/03 09:53:29 AM
MEDICAL OFFICER

Badrul Chowdhury
1/17/03 06:54:57 PM
MEDICAL OFFICER
I concur

TEAM LEADER MEMORANDUM

DATE: February 9, 2000

TO: NDA 20-800 TwinJect® Epinephrine Injection, USP (1:1000)

FROM: Badrul A. Chowdhury, MD, PhD
Acting Medical Team Leader,
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Secondary medical review of TwinJect®) response review

CC: HFD-570: Meyer, Nicklas, Jafari

Administrative

NDA2-800 was submitted to the Agency on December 5, 1996. Subsequently multiple submissions has been made to the NDA. During the time, the sponsor of this NDA has changed. At present Hollister-tier is the holder of the NDA. The proposed trademark name has been changed from — to TwinJect.

The latest submission to the NDA is dated August 16, 1999, which was a full response to our Deficiency Letter dated November 9, 1999. Deficiencies were primarily CMC related. Subsequently the sponsor has submitted a follow-up letter on December 13, 1999, in response to an information request. Issues dealt in the sponsor's latest submission deals with the CMC deficiencies. The CMC reviewer Dr. Chong-Ho Kim has recommended an approvable action pending resolution of the outstanding CMC issues, which are detailed in his review dated January 31, 2000.

Product description

TwinJect Epinephrine Injection, USP (1:1000), is a drug delivery system consisting of an automatic needle insertion/injection device and an existing — Epinephrine injection, US 1:1000. The device is designed to deliver two doses of 0.3 cc (0.3 mg) each subcutaneously or intramuscularly to patients — The first dose of epinephrine is delivered automatically by the auto-injector, while the second dose is delivered manually after the patient partly dismantles the device.

Clinical issues

As clinical support for this NDA, the sponsor had submitted a summary review, and 45 articles from the clinical literature dealing with the pharmacodynamics, pharmacokinetics, toxicology, and clinical efficacy of epinephrine in the treatment of anaphylaxis and asthma. It was determined earlier that the submission was adequate to support the efficacy and safety of epinephrine for treatment of life-threatening allergic reactions and asthma for patients

Outstanding clinical issues are primarily labeling. Labeling of currently marketed epinephrine-containing drug products with similar indications, such as Epi-pen and Anakit, is historically old and does not necessarily reflect the current literature on the use of epinephrine in life-threatening allergic reactions. The sponsor's proposed labeling of TwinJect is based on these outdated labels. Dr. Nicklas has recommended extensive modification of the sponsor's proposed label in his primary medical review. This secondary review concurs with those recommendations in principle. However, the TwinJect label needs to be further modified to not only update the scientific contents of the label, but also to make it as much consistent as possible with the labels of Epi-pen and Anakit. Epi-pen label appears to be more modern, and will be used as a model for some of the revisions.

Recommendation

From a clinical standpoint TwinJect® Epinephrine Injection, US (1:1000) is approvable based on well-defined effectiveness of epinephrine in the treatment of life-threatening allergic reactions, the demonstration that the device will deliver the drug product as claimed, and the relative safety of epinephrine under life-threatening circumstances. However, the labeling for this drug product needs extensive modifications for reasons outlined above. The label also needs to be made as much consistent as possible with the labels of Epi-pen and Anakit. Since this application will not be approved in this cycle because of CMC deficiencies, the final labeling will not be done at this time. For the purpose of records, Dr. Nicklas's labeling review will be placed in the action package. This will be used later as a starting point for final labeling. At this time the sponsor should be reminded of the need for a study to evaluate the time necessary for patients with disabilities, such as significant arthritis, to perform the procedures necessary for the second manually injected dose of epinephrine. If such study is not conducted, the label may indicate that the product is not suitable for patients with such disabilities.

DEC 4 1997

MEMORANDUM

DATE: December 3, 1997

TO: NDA 20-800 19

FROM: John K. Jenkins, M.D.
Director Division of Pulmonary Drug Products HFD-570

SUBJECT: Overview of NDA Review Issues

Administrative

NDA 20-800 for — (epinephrine injection 1:1000) was originally submitted by Bayer on December 6, 1996. The current user fee goal date for NDA 20-800 is December 6, 1997. — consists of an auto-injector device for patient self-administration of epinephrine injections subcutaneously or intramuscularly in the event of anaphylaxis and anaphylactoid reactions. The device is designed to administer one dose of epinephrine by a — mechanism. The patient can also disassemble the device and administer a second dose of epinephrine manually if necessary.

The epinephrine 1:1000 syringe contained in the device is the same epinephrine syringe currently marketed by — as a member of their — family of injectable drugs. This — epinephrine syringe is not the subject of an NDA (pre-1938 drug) and has never been approved by the FDA. As such, the FDA has access to very little information regarding the manufacturing, quality control, and stability testing of the marketed epinephrine syringe. Bayer has been asked to provide this information in support of their application, however, they have been unable to submit these data, at least in part due to a lack of cooperation from — In addition, a recent CGMP inspection of — demonstrated numerous violations of CGMPs for — products, including the epinephrine syringe. The use of a legally marketed, but unapproved, epinephrine syringe in the — device combined with the lack of cooperation of — in providing basic CMC information in support of the — NDA and the results of the recent CGMP inspection have resulted in the need to address some complex regulatory issues that impact directly on the approvability of this application.

A meeting was held on December 2, 1997, with participation from DPDP, ONDC (Dr. Gibbs and Dr.Chu), and ODE II (Dr. Bilstad) to discuss these regulatory issues. There was unanimous agreement at that meeting that in order for Bayer to secure approval for the — NDA, it would be necessary for them to provide adequate CMC information regarding the epinephrine syringe to allow the Agency to make a determination that the — device is safe, effective, and adequately labeled for marketing. It was also agreed that the fact that the — epinephrine syringe, which is currently legally marketed as a pre-1938 drug, is used as a component of the — product does not obviate the need for Bayer to provide basic CMC data on the epinephrine syringe to support approval of the

application.

As part of the discussion at the December 2, 1997, meeting, a discussion was held regarding what, if any, enforcement action the Agency should take against the [redacted] epinephrine syringe given the CGMP inspection report, the anedoctal reports that the [redacted] epinephrine syringe has a stability problem in that the epineprine solution degrades and changes color long before the stated expiration date is reached, and the fact that the Agency has decided that more CMC information regarding the epinephrine syringe is necessary before the Agency can conclude that the [redacted] device is safe and effective for marketing. It was noted that the Agency can take enforcement actions against pre-1938 drugs and has done so in the past when issues related to the safety and/or efficacy of the product have become apparent. It was agreed that there is a difference between an affirmative finding by the Agency that [redacted] which includes the [redacted] epinephrine syringe, is safe and effective for marketing approval under 1997 standards and initiation of a compliance enforcement action against the [redacted] epinephrine syringe which is legally marketed as a pre-1938 drug. It was agreed that ONDC will [redacted]

Clinical

The proposed indication for [redacted] (epinephrine injection 1:1000) is for treatment of severe allergic reactions, including anaphylaxis and anaphylactoid reactions, in response to exposure to bee stings, allergy injections, etc. and the treatment of severe, life-threatening asthma attacks. These indications are the same as those currently approved for other epinephrine 1:1000 injection products. The sponsor did not submit any clinical trials or clinical data in support of this application, instead the application is submitted as a 505(b)(2) application with reference to the finding of safety and efficacy made by the FDA for the Epi-Pen NDA. The absence of clinical data for this product is acceptable given that the only differences between this product and the [redacted] are related to the device itself and the epinephrine syringe used and are issues that can be adequately addressed by the submission of CMC data.

There are no outstanding clinical issues and the NDA is approvable from a clinical perspective with appropriate labeling. Review of the labeling will be deferred until the application is otherwise approvable.

Preclinical

The sponsor did not submit any non-clinical studies in support of this application. This is acceptable as epinephrine injection 1:1000 has a long marketing history in the U.S. and this 505(b)(2) application is relying on the Agency's finding of safety and effectiveness for Epi-Pen.

There are no outstanding issues and the NDA is approvable from a preclinical perspective with

appropriate labeling. Labeling negotiations with the sponsor will be deferred until the applicaiton is otherwise approvable.

CMC

Please see above under "Administrative" for a discussion of the CMC issues related to Anaguard 2. The sponsor has not submitted basic CMC information regarding the epinephrine syringe contained in the device, including adequate data on the synthesis of the epinephrine drug substance, impurities and degradation products testing in the drug substance, stability testing for the drug substance or the drug product, etc. Please refer to the review prepared by Dr. Kim for additional details regarding the CMC review of this application.

The application is not approvable from a CMC perspective. Outstanding CMC deficiencies which must be addressed prior to approval of the application will be included in the action letter to the sponsor.

Clinical Pharmacology and Biopharmaceutics

The sponsor did not submit any PK studies in support of this application. This is acceptable as this drug product is a solution for injection and the sponsor is relying on the Agency's finding of safety and effectiveness for the Epi-Pen NDA to support approval of this NDA.

There are no outstanding clinical pharmacology and biopharmaceutics issues and the application is approvable.

Data Verification

The Division of Scientific Investigations (DSI) was not asked to perform any audits for this NDA since no clinical or preclinical data were submitted in support of the application.

Labeling

The proposed trade name, — was found to be unacceptable by the LNC and the division due to the inclusion of the — in the product name which could result in confusion (i.e., it is not clear what the — refers to). The sponsor subsequently proposed the product be named as — or TwinJect. The LNC found the — name to be unacceptable as it is too similar to the USAN name — for another drug substance. The LNC and the division have no objections to the proposed name "TwinJect". Comments regarding other aspects of the proposed labeling will be deferred pending resolution of the outstanding CMC issues.

Conclusion

There are significant outstanding issues related to the CMC review of this product which must be resolved before this application can be approved. Therefore, the sponsor should receive a NOT APPROVABLE letter listing the outstanding CMC deficiencies. Labeling comments will be deferred pending acceptable resolution of these CMC issues.

cc:
NDA 20-800
HFD-570 Division Files
HFD-570/Jenkins
HFD-570/Schumaker
HFD-570/Toyer
HFD-570/Honig
HFD-570/Nicklas

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
DIVISION OF PHARMACEUTICAL EVALUATION II

Date: Jan. 17, 1997

To: Director, Mei-Ling Chen, Ph.D. (HFD-870)
Deputy Director, Mr. John Hunt (HFD-870)

Through: Team Leader, Dale Conner, Pharm.D. (HFD-870) _ /S/

From: Tien-Mien Chen, Ph.D. (HFD-870) /S/

RE: Filing Meeting for NDA 20-800 / — Epinephrine Injection USP)

SYNOPSIS:

Emergency epinephrine injection units have been marketed by Bayer for over 30 years in the Ana-Kit Anaphylaxis Emergency Kit form in many countries. Sales of the drug component, ———————, manufactured by ———— precede this time by many years. The AnaGuard (the same syringe unit in a "pen holder") was introduced in 1989. Both Ana-Kit and AnaGuard deliver two manual doses of epinephrine USP (1:1000). They are indicated for allergic reactions including 1) anaphylactic shock due to stinging insects, 2) severe allergic or anaphylactic reactions due to allergic injection, exposure to pollens, dusts, molds, foods, drugs, exercise, or unknown substances, and 3) severe life-threatening asthma attacks. However, it should be noted that although the drug component, ———————, was used for many years (a grandfather drug), it has never been approved by the Agency.

Note: EpiPen (epinephrine USP 1:1000) and EpiPen, Jr. (epinephrine USP 1:2000) with autoinjector that was filed under NDA 19-430 on 01/30/85 by Survival Tech Inc. was approved by the Agency on 12/22/87 for the same indications. The formulations of EpiPen and EpiPen Jr. (containing ———— are slightly different from that of epinephrine in — (without ———— Included in NDA 19-430 were literature articles for safety and efficacy review. No pharmacokinetic (PK) information on epinephrine was submitted. Nevertheless, NDA 19-430 has never been reviewed by The Office of Clinical Pharmacology and Biopharmaceutics/ Division of Pharmaceutical Evaluation II (OCPB/DPEII).

The — that was filed under NDA 20-800 on 12/05/96 by Bayer is an improved design which delivers the first dose (0.3 ml) of epinephrine automatically and the second dose (0.3 ml) manually, if needed. The same drug component, ———————— is used except the drug delivery system. Please see Figure 1 for the delivery system of

— for detail. No PK studies were submitted under Human Pharmacokinetics and Bioavailability section of this NDA. The PK information provided is obtained from two published articles. Please see the proposed package insert (PI; Oct, 96 version) in Attachment 1 for details.

According to the proposed PI, — . is to be given by — injection as the currently marketed Ana-Kit and AnaGuard. However, — . is different from Ana-Kit and AnaGuard in:

1. **Indications and Usage:**

   — is only indicated — and two fixed doses (0.3 ml) are to be given automatically (first) and then manually (second), if needed. Ana-Kit and AnaGuard are for patients from infants to adults and the two doses to be given manually are 0.3 ml for adults and children over 12 years; 0.2 ml for 6-12 years; 0.15 ml for 2-6 years; 0.05 to 0.1 ml for infants to 2 years.

2. **Dosage and Administration:**

   By IM or SC injection, — is to be given into the anteriolateral aspect of the thigh only, while Ana-Kit and AnaGuard are given into the deltoid region of the arm or the anteriolateral aspect of the thigh.

RECOMMENDATION:

— that was filed under NDA 20-800 on 12/05/96 by Bayer has been briefly reviewed by OCPB/DPEII. OCPB/DPEII is of the opinion that if the currently marketed epinephrine in — had been approved previously, it could have been used as an anchor to waive the submission of evidence of in vivo bioavailability or bioequivalence of this drug product, — However, it is a grandfather drug and has never been approved by the Agency. From a biopharm perspective, it is felt that since 1) the same drug component, epinephrine USP (1:1000) in — is to be used and 2) the drug solution is also to be given by IM or SC injection as the currently marketed Ana-Kit and AnaGuard, no bio-issues are expected. Therefore, the NDA is seemingly acceptable for filing. Nevertheless, the OCPB/DPEII has the following comment and the comment should be conveyed to the sponsor ASAP.

COMMENT: (Needs to be sent to the sponsor)

It is recommended that 1) a literature search be conducted for current pharmacokinetic (PK) information on epinephrine in humans and 2) the package insert be updated if additional PK information is available from literature and/or future PK studies.

cc: NDA 20-800, HFD-570 (Nicklas, Toyer), HFD-870 (M.L. Chen, D. Conner, T.M. Chen), HFD-850 for M. Millison (Drug).

CM

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

NDA 20-800 For AnaGuard2 (Epinephrine Injection USP)

Attachment 1:

Package Insert (Oct. 1996 version)

4 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

MEMORANDUM

DATE: May 28, 2003

TO: NDA 20-800 file

FROM: Chong-Ho Kim, Ph.D.
CMC Reviewer

THROUGH: Dr. Guirag Poochikian,

CC: Ms. Ladan Jafari

SUBJECT: CMC review of TwinJect™ (Epinephrine Injection, USP 1:1000) Auto-Injector; submission dated May 22, 2003

The most recent action was an Approvable action, which was taken on January 29, 2003. At that time all CMC issues had been resolved, with the exception of the Establishment Evaluation Review (EER).

The EER has now been completed and was acceptable (OC recommendation dated May 21, 2003). Therefore, the application is now acceptable for Approval from CMC standpoint.

Recommendation
Chemist recommends approval of this application.

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/s/

Chong-Ho Kim
5/28/03 11:52:54 AM
CHEMIST

Guiragos Poochikian
5/28/03 12:03:11 PM
CHEMIST

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 20800/000
Org Code : 570
Priority : 3S

Sponsor: HOLLISTER STIER LABORATORIES L
3525 NORTH REGAL ST
SPOKANE, WA 99207

Stamp Date : 06-DEC-1996
PDUFA Date : 29-JAN-2003
Action Goal :
District Goal: 06-AUG-1997

Brand Name : TWINJECT
Estab. Name:
Generic Name: EPINEPHRINE
Dosage Form: (INJECTION)
Strength : 3MG/ML

FDA Contacts:			
D. TOYER	Project Manager (HFD-420)	301-827-7609
C. KIM	Review Chemist (HFD-570)	301-827-1050
G. POOCHIKIAN	Team Leader (HFD-570)	301-827-1050

Overall Recommendation: ACCEPTABLE on 21-MAY-2003by J. D AMBROGIO(HFD-322) 301-827-9054

WITHHOLD on 28-JAN-2003by R. WOODS (HFD-322) 301-827-9011

ACCEPTABLE on 26-JUL-2001by J. D AMBROGIO(HFD-322) 301-827-9054

WITHHOLD on 25-JUL-2001by S. FERGUSON(HFD-322) 301-827-9009

WITHHOLD on 16-JUN-2000by HARTMANB

ACCEPTABLE on 26-OCT-1998by J. D AMBROGIO(HFD-322) 301-827-9054

WITHHOLD on 02-DEC-1997by EGASM

WITHHOLD on 26-NOV-1997by EGASM

Establishment : CFN : 1925262 FEI : 1925262
ABBOTT LABORATORIES
1776 NORTH CENTENNIAL DR
MCPHERSON, KS 67460

MF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-OCT-02

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 08-OCT-02

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 3010477 FEI : 3010477

HOLLISTER STIER LABORATORIES

3525 NORTH REGAL ST

SPOKANE, WA 99207

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-MAY-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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

[redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-OCT-02

Decision : ACCEPTABLE

eason : BASED ON PROFILE

Establishment : CFN : FEI :

[redacted]

101 GORDON STREET

LIONVILLE, PA 19341

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-OCT-02

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION
