CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-800

CORRESPONDENCE

Hollister-Stier
Laboratories LLC

P.O. Box 3145
Spokane, WA 99220-3145
Phone: 509 489-5656
Fax: 509 464-4320
www.hollisterstier.com

Date: May 30, 2003

To: Ladan Jafari
From: David Mirabell

Company: Division of Pulmonary and Allergy Drug
Fax: 509-482-3519

Fax: 301-827-1271
Phone: 509-482-1721

Phone: 301-827-1084
Pages: 1

May 30, 2003

Dear Ladan,

Re: NDA 20-800

In a phone conversation today you stated that Drug Safety had placed two additional requests pertinent to NDA 20-800.

These requests were:

- Make sure the established name is at least one-half the size of the proprietary name.

  Hollister-Stier will review and revise as necessary all copy before printing to assure this request is fulfilled.

- Increase prominence of the route of administration on product labeling.

  Hollister-Stier agrees to increase the prominence of the route of administration on pertinent product labeling prior to the time of printing.

Sincerely,

David L Mirabell
Director, Regulatory Affairs

Hollister-Stier Laboratories LLC
P.O. Box 3145
Spokane, WA 99220-3145
Phone: (509) 489-5656
Fax: (509) 484-4320

January 29, 2003

ORIGINAL

Badrul Chowdhury, M.D.
Acting Director
Division of Pulmonary and Allergy Drug Products HFD-570
Center for Drug Evaluation and Research
U. S. Food and Drug Administration
Document Control Room 10B03
5600 Fisher's Lane
Rockville, MD 20857

RECEIVED
JAN 29 2003
FDR/CDER

ORIG AMENDMENT

N-000 BL

RE: NDA 20-800 - Twinject™ Auto-Injector Epinephrine Injection USP (1:1000)
Amendment - Response to Labeling Comments and Agreement to Labeling Changes.

Dear Dr. Chowdhury:

Reference is made to our pending New Drug Application, NDA 20-800, for Twinject™ Auto-Injector, submitted on December 5, 1996, and amended for the — Epinephrine on June 26, July 17, August 15, September 28, October 29, and December 18, 2001; and on February 6, June 1, July 26, September 24, September 25, November 4, and December 13, 2002.

This Amendment is to acknowledge that Hollister-Stier Laboratories LLC (HSL) agrees to labeling comments received in a telephone conversation with Ladan Jafari of the Division on January 24, 2002 . FDA comments and HSL responses are as follows:

All Labels and Labeling

FDA Comment

The Twinject proprietary name is represented in more that one color. Use only one color in the proprietary name throughout the labels and labeling.

HSL Response

HSL agrees to change the Twinject proprietary name on all labels and labeling to a single color.

Individual Carton and Labels

FDA Comment

Provide measured dimensions of the individual carton and the labels.

HSL Response

The measured dimensions of the individual carton and labels are provided, as follows:

Individual Carton: [redacted] folded)
– Epinephrine Label: [redacted]
Case Bottom Label: [redacted]
Patient Label: [redacted]

Physician's Instructions (PI)

FDA Comment

The change proposed in the redline copy provided by HSL in the transmittal via e-mail of 12/13/02 is acceptable with no further change. Send a clear copy.

HSL Response

A clear copy of the Physician's Instructions is attached.

Patient Information (PPI)

FDA Comment

The changes proposed by HSL in the redline copy provided in the labeling transmittal via e-mail of 12/13/02 are acceptable, provided that the following additional changes are made. On page 1 of the PPI, change the sentence which reads [redacted] .' to read [redacted]

HSL Response

HSL agrees to change the wording as indicated.

FDA Comment

On page 2 of the PPI, under the heading '[redacted], change the sentence which reads '[redacted] to read [redacted]

HSL Response

HSL agrees to change the wording as indicated.

FDA Comment

On page 2 of the PPI, under the heading '[redacted], change the sentence which reads '[redacted] to read '[redacted]

HSL Response

HSL agrees to change the wording as indicated.

FDA Comment

On page 4 of the PPI, in Step 2 of the patient directions, change sentence 3, which reads '[redacted] o read '[redacted]

HSL Response

HSL agrees to change the wording as indicated.

FDA Comment

On page 4 of the PPI, in Step 2 of the patient directions, change sentence 4, which reads '[redacted] to read '[redacted]

HSL Response

HSL agrees to change the wording as indicated.

Case Bottom Label

FDA Comment

The copy of this label submitted on August 15, 2002 is acceptable, with the following additional change: The words '(epinephrine injection) USP 1:1000' should appear more prominent in relation to the words '

HSL Response

HSL agrees to change the appearance of the established name '(epinephrine injection) USP, 1:1000' or the warning '
, or both statements, so that the prominence is acceptable to the Agency.

Patient Label

FDA Comment

The copy of this label submitted on August 15, 2002 is acceptable, provided that the following additional changes are made:

In of the patient directions, change sentence 3, which reads

HSL Response

HSL agrees to change the wording as indicated.

FDA Comment

In of the patient directions, change sentence 4, which reads '
.' to read

HSL Response

HSL agrees to change the wording as indicated.

As requested by Ms. Jafari in the telephone conversation referred to above, revised copy of the Prescribing Information and the Patient Information are attached to this facsimile. Also, as requested, revised copy of all labeling and labels will be submitted on electronic media to the Central Document Room as soon as the revised copy electronic files are available.

Please contact me at Hollister-Stier Laboratories LLC, in Spokane, WA, if you have any questions or comments. I can be reached at 509-482-1721.

Sincerely Yours,

David L. Mirabell
Director, Regulatory Affairs and Professional Services
Hollister-Stier Laboratories LLC

Attachments

7 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

NDA 20-800

Dear Mr. Eddy:

We are reviewing your NDA for Twinject and have the following comments and questions. Please address these as soon as possible. The comments in the brackets refer to your response dated July 26, 2002.

1. Modify the stability commitment on page 70. See comments #8 of the Agency's non-approval letter dated December 4, 1997, and #8(a) of the Agency's approvable letter dated February 15, 2000. [Response 3(a)]

2. The following comments pertain to Response 5.

   a. Express acceptance criteria for individual [redacted] and total [redacted] in microgram per component's weight.

   b. Tighten the leachable limit for [redacted] to NMT [redacted]

   c. We remind you of the following Phase 4 commitments. [redacted]

3. Tighten the release limit for chlorobutanol to [redacted] [Response 6(a)(2)]

4. Provide updated stability protocol to incorporate the modifications stated above. Insert a footnote that the proposed acceptance criteria for [redacted] are per formulation weight.

5. Provide updated specifications for Twinject™ Auto-Injector.

6. Provide three copies of method validation packages.

If you have any questions, I may be reached at 301-827-1084.

LJ

Ladan Jafari, Regulatory Project Manager

Initialed by: Barnes/12-3-02
KimCh/12-3-02
Poochikian/12-3-02

Filename: Twinject CMC comments.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
12/4/02 08:04:02 AM
CSO

NDA 20-800
Drug: Twinject
Applicant: Hollister-Stier Laboratories
Date of Telecon: June 17, 2002

Hollister-Stier Laboratories Representatives:

Terance Kordash, M.D., Vice President, Scientific & Medical Affairs
David Mirabell, Director, Regulatory Affairs & Professional Services
Derek Constable, Ph.D., Director, New Product Discovery
Shirley Williamson, Director, Quality Assurance
Jerry Eddy, M.S. Regulatory Affairs Scientist
[redacted], Consultant to Hollister-Stier Laboratories

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

Ladan Jafari, Regulatory Project Manager
Chong-Ho Kim, Ph.D., CMC Reviewer
Guirag Poochikian, Ph.D., CMC Team Leader

Background: Hollister-Stier Laboratories submitted a request for a telecon to discuss the proposal for resolving deficiencies cited in the approvable letter dated December 18, 2001, regarding test methods and specifications for [redacted], from the [redacted] components, test method for [redacted], in the drug product, and test method for chlorobutanol in the drug product. Questions raised by Hollister-Stier Laboratories are printed in Italics below followed by the Division's responses and discussions.

The Division initiated the telecon by first indicating that it was very difficult to review and follow the briefing the package due to lack of pagination, and requested that in the future submissions, Hollister-Stier Laboratories properly identify and paginate each section.

1. *Is the proposed approach to test methods and specifications for [redacted] from the [redacted] components acceptable?*

- The Division stated that the [redacted] of [redacted] too low. The Division indicated that [redacted] should be done in [redacted] The Division referred to USP general chapter <381> for Physicochemical Test Procedures in [redacted] for Injections.

  - Hollister-Stier Laboratories raised concerns that pH may not be accurate, if they [redacted] under such temperatures. Hollister-Stier Laboratories asked if they could [redacted] for a longer duration.

- The Division disagreed with [redacted], and stated that in order to obtain a reliable [redacted] profile, the [redacted] study should be done at higher temperatures, e.g., [redacted] using suitable system and techniques.

➢ Hollister-Stier Laboratories indicated that they would provide the data on [redacted] time points. Hollister-Stier Laboratories also indicated that the [redacted] data show a linear decrease in the [redacted] levels (about [redacted] for [redacted] and about [redacted] for [redacted]). Hollister-Stier Laboratories agreed to provide the data to the Division for review.

3. *Is the proposed approach to test method for chlorobutanol in the drug product acceptable?*

- The Division asked that Hollister-Stier Laboratories provide justification for the increase of [redacted] of chlorobutanol levels in [redacted], and give the LOD and LOQ of the method.

  ➢ Hollister-Stier Laboratories indicated that they would provide the justification in the response letter.

Drafted by:: LJ/6-20-02

Initialed by: KimCH/6-20-02
Poochikian/6-26-02

Filename:Hollistermtgmin

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
6/27/02 01:16:15 PM
CSO

NDA 20-800 Twinject
Sponsor: Hollister-Stier Laboratories
Date of Telecon: February 21, 2002

Hollister-Stier Laborarories Representatives:

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

Background: Hollister-Stier submitted a request for a telecon to discuss the data needed to remedy the deficiencies cited in the approvable letter dated December 18, 2001. Hollister-Stier also wanted to discuss some of the points discussed at a face to face meeting dated January 23, 2002. The following points printed in Italics below are the steps that Hollister-Stier is planning to take to remedy the deficiencies.

1. *Develop, validate, and verify specific test methods appropriate for relevant potential listed by for the*

2. *Generate profile for formulation under stress condition ( ) using and drug product placebo/vehicle as , for the potential listed above (should additional be observed, investigations will be conducted to identify and quantitate, if appropriate). lots of formulation will be analyzed.*

3. *The proposed are believed to be in conformance with the recommendation of*

Based on studies performed in 2 above, propose appropriate methods with limits for individual

- The Division asked how Hollister-Stier concluded that the above compounds were the and what vehicles were used in studies. Hollister-Stier replied that they used the drug product, and they also used the to obtain the above

  - The Division advised Hollister-Stier to also use other such as generate an profile. The Division also asked that the proposed analytical method for the profiles be validated.

- Hollister-Stier indicated that other solvents may generate other that are not in the drug product. Hollister-Stier stated that according to the guidance document for study, they do not see any reason why they should try other

  - The Division asked that Hollister-Stier refer to the guidance document for , and pay particular attention to the section that refers to study for The Division stated that Hollister-Stier should first establish ar profile and then identify the observed peaks. The proposed method should then be used in studies. The purpose of to establish the adequacy of the analytical methods and the verification of the compositional consistency of the incoming materials. The Division asked if Hollister-Stier was planning on developing a methodology for any of the above dentified so far. Hollister-Stier stated that they are developing a methodology for at this point. The Division stated that if Hollister-Stier has data to demonstrate that the identified do not have any adverse effect on stability, then they do not need to do any additional studies.

- The Division emphasized the importance of verifying the methods and the results by a 3rd lab. This quality check does not need to be performed on every batch, but should be established initially and verified periodically upon a mutually agreed upon schedule. Hollisterr-Stier asked if they could submit the application without the verification of the 3rd lab. The Division responded that as long as the 3rd lab has been identified and the response to the approvable letter states that they would do the periodic verification and the requested information will immediately follow the submission, Hollister-Stier can resubmit the application.

- Hollister-Stier asked how they should propose a limit, and what would a limit of detection be for —

  - The Division responded that Hollister-Stier should look at the sensitivity and other attributes of the method, and report the actual levels. This information should be based on appropriate method validation. (See ICH doucments Q2A and Q2B for additional guidance.)

4. *Provide — data for the above listed — for — Epinehprine stability samples, real time and accelerated (and for subsequent time points). Commit to testing the — lots intended for commercial distribution.*

5. *Upon commercial introduction, perform — test on — lot of — — according to the procedure and limits developed from number 3 above.*

   - The Division agreed with both proposals identified in number 4 and 5 above. The Division stated that since — is not doing the — study, then Hollister-Stier should perform the — study on every batch using appropriate acceptance criteria, and this information should be included as part of the acceptance criteria in the NDA submission.

The Division asked when Hollister-Stier was planning on submitting the NDA, and Hollister-Stier indicated that it might take them another 4 months before they can finalize all the issues.

NDA 20-800 Twinject
Sponsor: Hollister-Stier Laboratories
Date of Telecon: February 21, 2002

Initialed by: Kim3-15-02
Poochikian/3-22-02

Filename: Twinjecttcon.doc

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/s/

Ladan Jafari
3/25/02 03:57:29 PM
CSO

NDA 20-800

We have received your submission dated March 29, 2001, which contains responses to our action letter of September 14, 2000, and we have the following preliminary comments. There is not sufficient information on [redacted] its stability, and performance characteristics of the device with [redacted] in the submission to allow for review. Therefore, this submission will be classified as a minor amendment. Submit a complete package when the requisite information is available.

1. Comments 1 and 2 of the action letter were raised for [redacted] which is manufactured by [redacted] However, since the [redacted] is no longer availabe, to establish [redacted] as a source for epinephrine solution, provide the following information.

   a. Complete CMC information about epinephrine.

   b. Manufacture and control, test method and acceptance criteria, stability protocol and data

   c. Components and composition, [redacted] data of the container and closure system.

   d. Performance test, functional test, and stability data of the Twinject with [redacted]

   e. Since the [redacted] is no longer available for your drug product (Twinject), what was agreed on the [redacted] may not be applicable. New data are needed to support the new container closure system. Additionally, withdraw [redacted] from the current application.

   f. A Letter of Authorization (LOA) to refer to the appropriate DMF that includes all the pertinent information on the [redacted] system.

2. Your responses to comments 3 and 4 of the action letter are not adequate. Provide performance test, functional test, and stability data of the Twinject with [redacted]

3. Since no stability data are available for [redacted] epinephrine ([redacted] and for the drug product (Twinject with [redacted]), generate new sets of data and provide a revised stability protocol. (Response 5)

4. When you amend the submission, replace the word [redacted] with [redacted] where it is applicable, e.g., in SOPs, test methods and specification.

5. Provide assurance that the needle length and hence the depth of drug delivery will not change with the use of the new [redacted]. The performance of the new device with the [redacted] must be the same as has been shown with the [redacted] in regard to use through clothing and use by disabled individuals. It is important that the delivery of additional doses be feasible in an emergent setting.

If you have any questions, please contact me at 301-827-5584.

Ladan Jafari, Regulatory Project Manager

cc:

HFD-570 Div.files
HFD-570/Nicklas
HFD-570/Chowdhury
HFD-570/Sun
HFD-570/Kim
HFD-570/Poochikian

Initialed by: Barnes/4-19-01
Meyer/4-19-01
Kim/4-20-01
Poochikian/4-20-01

Filename:N20800/3-29response

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/s/

Ladan Jafari
4/20/01 10:27:19 AM
CSO

ORIGINAL

Bayer

Pharmaceutical Division

Allergy Products

Bayer Corporation
P.O. Box 3145
Spokane, WA 99220-3145
Phone: 509 489-5656
Fax: 509 484-4320

April 18, 1997

Dr. John Jenkins, Director
Division of Pulmonary Drug Products, HFD-570
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 10B03
5600 Fishers Lane
Rockville, MD 20857

RE: NDA #N020800 for — Epinephrine Injection USP (1:1,000)

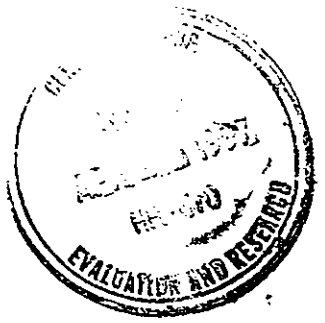
Dear Dr. Jenkins:

Pursuant to Section 306(k) of the Food, Drug, and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Bayer Corporation , Pharmaceutical Division, Allergy Products makes the following declaration.

After review of the April 6, 1997 Debarment List, Bayer Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the act, in connection with the above referenced application.

Sincerely,

David L. Mirabell
Manager, Regulatory Affairs



N(XR)

DUPLICATE

Bayer

Pharmaceutical
Division

Allergy Products

Bayer Corporation
P.O. Box 3145
Spokane, WA 99220-3145
Phone: 509 489-5656
Fax: 509 484-4320

January 27, 1997

Dr. John Jenkins, Director
Division of Pulmonary Drug Products, HFD-570
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control 10B03
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-800 for — Epinephrine Injection USP (1:1000), Patent Certification

Dear Dr. Jenkins:

In accordance with 505(b)(2) of the Food, Drug, and Cosmetic Act, Bayer Corporation certifies that to the best of our knowledge, there are no patents that claim the drug Epinephrine Injection, USP (1:1000), or its use.

The Bayer 505(b)(2) application is based upon the FDA listed reference product, Epi-Pen Auto-Injector (Epinephrine Injection), Survival Technology, Inc., NDA 19-430.

Sincerely,

David L. Mirabell
Manager, Regulatory Affairs
DLM/tmc

Bayer

Pharmaceutical Division

Allergy Products

Bayer Corporation
P.O. Box 3145
Spokane, WA 99220-3145
Phone: 509 489-5656
Fax: 509 484-4320

December 4, 1996

Dr. John Jenkins, Director
Division of Pulmonary Drug Products, HFD-570
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control
12229 Wilkins Avenue
Rockville, MD 20852

RE: NDA #N020800 for — Epinephrine Injection USP (1:1000)

Dear Dr. Jenkins:

This letter responds to a phone contact made by Ms. Denise Toyer on December 1, 1997, in which she requested that Bayer resubmit a patent certification regarding the reference listed drug EPIPEN®. This letter is a replacement for the Bayer certification letter of December 12, 1996 which addressed patent certification of the drug substance, Epinephrine Injection, U.S.P.

In accordance with Section 505(b)(2) of the Food, Drug, and Cosmetic Act, Bayer certifies that to the best of our knowledge, patents for the reference listed drug EPIPEN® have expired, and that there are no patent restrictions in the manufacture of the drug product presented in NDA #N020800.

Sincerely,

David L. Mirabell
Manager, Regulatory Affairs

Bayer

Pharmaceutical Division

Allergy Products

Bayer Corporation
P.O. Box 3145
Spokane, WA 99220-3145
Phone: 509 489-5656
Fax: 509 484-4320

October 28, 1996

Dr. John Jenkins
Director
Division of Pulmonary Drug Products, HFD-570
Food and Drug Administration
Parklawn Bldg., Document Room 10B-03
5600 Fishers Lane
Rockville, MD 20852

Dear Dr. Jenkins:

RE: Summary of Pre-NDA Meeting
March 6, 1996

Bayer is assembling the NDA for the drug/autoinjector unit which was described to you and your staff in a March 6, 1996 meeting. This letter is to reiterate our understanding of the outcome of that meeting, and thus will form the basis for the content of the upcoming NDA filing.

Dr. Derek Constable, Dr. Nancy Motola, ——— and myself represented Bayer at the pre-NDA meeting.

Outcomes are listed as follows:

1. NDA: 505(b)(2) NDA
2. Chemistry, Manufacturing and Control Section: There are two primary components of this product and they would be addressed as follows:
   a. ——— Epinephrine in their ——— brand system (Currently marketed by ———. NDA will contain the following:
      i. Change control letter from ———
      ii. DMF access letter from active substance manufacturer.
      iii. DMF access letter from ———
      iv. ——— batch manufacturing records.
      v. ——— analytical and biological control procedures.
      vi. Stability data.

b. Autoinjector Device which will contain the epinephrine

i. Bayer will provide complete details regarding component specifications, and manufacturing and control documentation for the device.

ii. Performance test criteria as detailed in our January 18, 1996 letter to your office, and which was reviewed in the March meeting.

iii. Incorporate elevated stability studies of approximately 6 months as requested by your staff.

iv. Include a non-invasive study of the autoinjector which will address the time it will take a subject to prepare the unit for a second injection, as requested by your staff.

v. Final product labeling, and package insert proof copy.

3. Pharmacology/Toxicology Section: To contain published references with a brief review.

4. Clinical Section: To contain published references with a brief review.

The NDA to be presented will abide by the rules for format of a NDA presented in the Code of Federal Regulations.

Bayer looks forward to working with your staff during the review process.

Sincerely,

David L. Mirabell
Manager, Regulatory Affairs
DLM/KRF

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Memorandum of Telephone Facsimile Correspondence

Date: 10/8/98

To: Mr. David Mirabell
Director, Regulatory Affiars

From: Dr. Denise P. Toyer
Project Manager

Subject: Not Approvable Letter

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

/S/

Denise P. Toyer
Project Manager
Division of Pulmonary Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-800

NOV - 9

Bayer Pharmaceutical Division
3525 N. Regal Street
Spokane, Washington 99207

Attention: David Mirabell
Manager, Regulatory Affairs

Dear Mr. Mirabell:

Please refer to your new drug application (NDA) dated December 5, 1996, received December 6, 1996, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for epinephrine injection 1:1000.

We acknowledge receipt of your submissions dated June 17, July 16, and August 24, 1998. Your submission of May 29, 1998, constituted a full response to our December 4, 1997, action letter.

We have completed our review of this application, as amended, and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows.

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] 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.

   b. Although a report (—) from [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.

   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.

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

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

2. 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).

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.

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

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

d. The total length of the — is limited to NLT — inches. The upper limit should also be provided.

e. The acceptance criteria for the distance between the top of the — and the top of the — is limited to NLT — The upper limit should also be provided.

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

g. Table 1 (July 16, 1998, amendment) indicates that the mean for the firing force is — . Therefore the specification should be significantly tightened to reflect the data, e.g., — (May 29, 1998, amendment, response 3).

4.

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 [redacted] NMT [redacted] 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.

The following preliminary comment pertains to the labeling. Additional comments will be provided when the above issues have been addressed.

6. The statement " [redacted] " on the TwinJect Carrying Case Label, as well as on the carton label should be changed to ' [redacted] " to avoid any confusion.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved. We strongly encourage you to request a meeting with this Division prior to submitting your response to this letter.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Dr. Denise Toyer, Project Manager, at (301) 827-5584.

Sincerely,

LS

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-800
HFD-570/Div. Files
HFD-570/Toyer
HFD-570/Nicklas/11-5-98
HFD-570/Kim/11-5-98
HFD-570/Sun/11-05-98
HFD-570/Chen/11-05-98
HFD-570/Honig/11-6-98
HFD-570/Poochikian/11-5-98
HFD-570/Uppoor/11-05-98
HFD-002/ORM
HFD-102/ADRA
HFD-95/DDMS
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: TOYER/November 4, 1998
Initialed by: Schumaker/11-5-98
Honig/11-6-98
Poochikian/11-5-98
Sun/11-5-98
Uppoor/11-5-98
Jenkins/11-6-98
final: Campbell/11-6-98
filename: c:\mydocuments\ongoing\n20800.11-00-00

NOT APPROVABLE (NA)

Jafari

OCT - 6 1999

NDA 20-800

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

Attention: David L. Mirabell
Manager, Regulatory Affairs

Dear Mr. Mirabell:

We acknowledge receipt on August 17, 1999, of your August 16, 1999, resubmission to your new drug application (NDA) for — epinephrine) Injection.

This resubmission is in response to the deficiencies cited in our November 9, 1998, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is February 17, 2000.

If you have any questions, contact Ms. Ladan Jafari, Project Manager, at (301) 827-5584.

Sincerely,

Cathie Schumaker, R.Ph.
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-800
HFD-570/Div. Files
HFD-570/Jafari
HFD-570/Schumaker
HFD-570/Kim
HFD-570/Poochikian
HFD-570/Nicklas
HFD-570/Chowdhury
DISTRICT OFFICE

Drafted by: LJ/October 4, 1999

Initialed by: Schumaker/10-5-99

filename: N20800AC

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)
(DDR: Update the user fee goal date based on the class of resubmission.)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
MEMORANDUM

DATE: December 1, 1997

FROM: Denise P. Toyer, R.Ph.
Project Manager

SUBJECT: Bioavailability and Clinical Issues

THRU: Richard Nicklas, M.D.
Clinical Reviewer

Peter Honig, M.D.
Clinical Team Leader

TO: NDA 20-800

In vivo Bioavailability

The new drug application for this NDA was submitted as a 505(b)2 application. The unpublished draft guidance document on 505(b)2 applications states the following:

- A 505(b)2 application should contain an in vivo study to compare the proposed product to the reference listed drug.

This sponsor did not conduct a bioavailability study. Under 21 CFR 320.22(e), the Agency may waive the requirement for the submission of evidence of in vivo bioavailability if the waiver is compatible with the protection of the public health.

The requirement for a bioavailability study is waived for the following reasons.

1. The [redacted] device will contain epinephrine [redacted] 1:1000. This product is marketed in the United States for the same indication that the sponsor is requesting for this application.

2. The drug product is a parenteral solution intended solely for administration by injection.

Clinical Issues

The sponsor did not submit any clinical studies for review. The use of epinephrine 1:1000 in the treatment of allergic reactions is considered standard emergency treatment for the indications proposed by the sponsor. The proposed indications for the use of [redacted] are:

[redacted]

This application is not approvable based on chemistry, manufacturing and control (CMC) deficiencies. Therefore the labeling for this product will be reviewed by the medical officer once these deficiencies are addressed by the sponsor.

cc:

Original NDA 20-800
HFD-570/Division File
HFD-570/Nicklas/12-3-97
HFD-570/Honig/12-3-97
HFD-570/Kim
HFD-570/Williams
HFD-570/Toyer

Initialed by: Schumaker/12-2-97

n:\nda\20800\pm\97-12-01.mem

NDA 20-800

Hollister-Stier Laboratories LLC
3525 N. Regal Street
Spokane, Washington 99207

Attention: David L. Mirabell
Manager, Regulatory Affairs
Official Correspondent

Dear Mr. Mirabell:

We acknowledge receipt on June 22, 1999, of your June 21, 1999, correspondence to the following new drug application (NDA) notifying the Food and Drug Administration that the corporate name has been changed from:

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

to:

Hollister-Stier Laboratories LLC
3525 N. Regal Street
Spokane, Washington 99207
Attention: David L. Mirabell

for the following new drug application: NDA 20-800 for epinephrine injection 1:1000.

Our records have been revised to reflect this change.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary Drug Products, HFD-570
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions please contact Ms. Ladan Jafari at (301) 827-1054.

Sincerely,

Denise Toyer, R.Ph., Pharm.D.
Project Manager
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-800
HFD-570/Div. Files
HFD-570/Toyer
HFD-570/Nicklas
HFD-570/Kim
HFD-570/Sun and Team Leaders
DISTRICT OFFICE

Drafted by: Toyer/6-28-1999
Initialed by: Schumaker/6-29-99
final:
filename: a:/letters/N20800.99-06-00

CHANGE OF NAME/ADDRESS (XA)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-800

DEC 4 1997

Bayer Pharmaceutical Division
3525 N. Regal Street
Spokane, Washington 99207

Attention: Mr. David L. Mirabell
Manager, Regulatory Affairs

Dear Mr. Mirabell:

Please refer to your new drug application dated December 5, 1996, received December 6, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for epinephrine injection 1:1000.

We acknowledge receipt of your submissions dated January 10 and 27, February 14 and 24, April 3, 9, and 18, May 29, September 5, October 1, November 10, and December 4, 1997. Please be advised that the November 10, 1997, pharmacology and toxicology amendment has not been reviewed prior to the issuance of this letter. The user fee goal date for this application is December 6, 1997.

We have completed our review of the submissions as noted above and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

1. The amendment to DMF [redacted] dated June 25, 1997, has been reviewed and remains inadequate. A letter dated September 22, 1997, was sent to the DMF holder listing the deficiencies.

2. In response to our request to provide specifications and test methods for impurities/degradation products (individual and total), you stated that the [redacted] was

   Please provide the requested information and data.

3. The firing force specification should be tightened to reflect your data.

4. You have stated that you are working with [redacted] to provide the requested information on the immediate container/closure system [redacted] epinephrine) in regard to composition and appropriate specifications and test methods. Please either provide the above information in the application or make reference to authorized DMFs for the same information.

The following comments pertain to the proposed stability protocol.

5. As stated in our May 5, 1997, letter, the room temperature condition should be specified by temperature and humidity.

6. Sterility, pyrogenicity, and degradation products tests should be included in the stability test parameters.

7. [redacted] tests are grouped together under [redacted] test. These tests should have their own specifications and test methods. Considering the instability of epinephrine, there should be a [redacted] test and specification.

8. The stability protocol should include the following three stability commitments.

   a. Bayer will monitor the stability of the [redacted] batches, and at least [redacted] batch [redacted] for the length of the expiration dating period.

   b. Stability testing will be performed according to the approved protocol and the results will be submitted periodically or as specified by the Agency.

   c. Bayer agrees to withdraw from the market any batch found to fall outside of the approved specifications for the drug product. If Bayer believes the deviation is a single occurrence that does not affect the safety and effectiveness of the drug product, Bayer agrees to discuss the deviation with the Division promptly.

9. Your proposed trademarks for the drug product, "TwinJect" and — , have been reviewed. — has been found to be unacceptable. This name is too similar to an authorized USAN name and may cause confusion among healthcare practitioners. TwinJect has been tentatively found to be an acceptable trademark. We remind you that the trademark review will be finalized at the time of approval of the NDA.

Labeling comments will be forwarded following satisfactory resolution of the above deficiencies.

During the recent inspection for your NDA of the — manufacturing facility, a number of deficiencies were noted and conveyed to your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, please contact Ms. Denise Toyer, Project Manager, at (301) 827-5584.

Sincerely yours,

[illegible] Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-800
HFD-570/Div. files
HFD-002/ORM
HFD-102/Office Director
HFD-101/L.Carter
HFD-820/ONDC Division Director
DISTRICT OFFICE
HFD-92/DDM-DIAB
HFD-570/D.Toyer
HFD-570/Jenkins
HFD-570/Honig
HFD-570/Nicklas
HFD-570/Poochikian
HFD-570/Kim
HFD-570/Sun
HFD-570/Williams
HFD_570/Wilson
HFD-570/Gebert
HFD-570/Conner
HFD-570/Chen

Drafted by: Toyer/November 18, 1997
Initialed by: Chen/12-2-97
Conner/12-3-97
Williams/12-2-97
Sun/12-2-97
Gebert/12-3-97
Wilson/12-3-97
Nicklas/12-3-97
Honig/12-3-97
Kim/12-3-97
Poochikian/12-3-97
Jenkins/12-3-97

final: WilsonP/12-04-97

NOT APPROVABLE (NA)

n:staff\toyerd\n20800.let

MESSAGE CONFIRMATION

12/04/97 20:01
ID=PULMONARY DIV FDA

NO.	MODE	BOX	GROUP
764	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
12/04 20:00	01'10"	509 484 4320	004/004	OK		0000

Memorandum of Telephone Facsimile Correspondence

Date: 12/04/97

To: David L. Mirabell
Manager, Regulatory Affairs

From: Denise P. Toyer
Project Manager

Subject: Action Letter

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

51

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-800

MAY 5 1997

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

Attention: David L. Mirabell
Manager, Regulatory Affairs

Dear Mr. Mirabell:

Please refer to your pending December 5, 1996 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anaguard2 (epinephrine) Injection, 1:1000.

We also refer to your amendments dated January 10, February 14, April 3 and 9, 1997.

We have completed our review of the chemistry, manufacturing and controls portion of your submission and have identified the following deficiencies.

The following comments pertain to the drug substance.

1. We have reviewed DMF [redacted] for the drug substance, [redacted] and found it inadequate to support NDA 20-800. The DMF holder was notified of our comments on March 18 and April 16, 1997.

2. Acceptance specifications and test methods at [redacted] for the bulk epinephrine manufactured by [redacted] should be provided.

Comments 3-5 pertain to the regulatory specifications and test methods for the drug product.

3. Specifications and test methods for impurities/degradation products (individual and total) for the [redacted] epinephrine should be provided (See Comment 7 below).

4. Total length of [redacted] and Distance between [redacted] and [redacted] have only lower limits. The target values and upper limits should be provided.

5. The following performance characteristics of the drug product should be addressed. Appropriate specifications should be established/modified to reflect the actual data for the following parameters.

   a. Needle protrusion beyond [redacted] should also have a target value and lower limit.

   b. Firing force [redacted] should be tightened.

   c. Volume for dose-1 and dose-2 should be established.

6. Information on the immediate container/closure system [redacted] epinephrine) should be provided. Composition and appropriate specifications and test methods should be included in the application. Authorized references could be made through appropriate letter(s) of authorization.

The following comments pertain to stability of the drug product.

7. We remind you of your commitment to provide information on degradation product profile, specifications, test methods and data on the Epinephrine Injection, USP 1:000 [redacted] by August 1997.

8. Comments on the proposed expiration dating period for [redacted] will be deferred until the stability data (chemical and mechanical) are submitted and evaluated.

9. The proposed stability protocol should be revised as follows.

   a. The room temperature conditions should be specified (temperature and humidity).

   b. Sterility, pyrogenicity, and degradation products tests should be included in the stability parameters.

   c. [redacted] tests should have separate specifications and test methods. Appropriate quantitative specifications and test method for [redacted] need to be established.

d. A modified stability protocol should be submitted which reflects the above comments. The stability protocol should include test parameters, test conditions, test methods, time points, and specifications. In addition, the stability protocol should provide the three points stability commitment. (Please refer to the stability guidance published in 1987.)

10. The name _ — is unacceptable. The use of numerical suffixes to reflect duration of effect, dosage strength, number of doses, or a suggested regimen is discouraged. Please provide a new trademark for this product.

We would appreciate your prompt written response so we can continue our evaluation of your NDA. Please note, however, that while we are providing these comments to you at this time in order to allow you as much time as possible to address them, providing a response to these comments will not necessarily preclude the issuance of an action letter.

If you have any questions, please contact Ms. Denise Toyer, Project Manager, at (301) 827-1089.

Sincerely yours,

/S/

John K. Jenkins, M.D.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-800
HFD-570/Div. Files
HFD-570/Toyer
HFD-570/Kim
HFD-570/Poochikian
HFD-570/Williams
HFD-570/Nicklas
HFD-820/ONDC Division Director

R/D BY: DToyer/04-23-97
Initialed by: Schumaker/04-24-97
Kim/04-24-97
Poochikian/04-24-97
final: PWilson/04-28-97

N:\staff\toyerd\n20800.cmc

INFORMATION REQUEST (IR)

Toyer

Memorandum of Telephone Facsimile Correspondence

Date: February 4, 1997

To: David L. Mirabell
Manager,
Regulatory Affairs

From: Denise P. Toyer
Project Manager

Through: Cathie Schumaker
Chief, Project Management Staff

Subject: NDA 20-800, Information Request

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

Denise P. Toyer
Project Manager
Division of Pulmonary Drug Products

NDA 20-800

The following clinical pharmacology and biopharmaceutics request is in response to a preliminary review of NDA 20-800 which was submitted on December 6, 1996.

Please provide:

1. a literature search for current pharmacokinetic (PK) information on epinephrine in humans, and

2. an updated package insert if additional (PK) information is available from the literature and/or future PK studies.

Please respond to these comments as soon as possible. If you have any questions, please contact Ms. Denise Toyer, Project Manager, at (301) 827-1089.

CC:
Orig. NDA 20-800
HFD-570 DIV. FILE
HFD-570/NICKLAS
HFD-570/KIM
HFD-570/WILLIAMS
HFD-570/TOYER

N:\NDA\20800\PM\97-02-00.FAX

MESSAGE CONFIRMATION

02/05/97 16:06
ID=PULMONARY DIV FDA

NO.	MODE	BOX	GROUP
364	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
02/05 16:05	00'41"	509 484 4320	002/002	OK		0000

Memorandum of Telephone Facsimile Correspondence

Date: February 4, 1997

To: David L. Mirabell
Manager,
Regulatory Affairs

From: Denise P. Toyer DPT
Project Manager

Through: Cathie Schumaker CS
Chief, Project Management Staff

Subject: NDA 20-800, Information Request

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you

RECORD OF TELEPHONE CONVERSATION

NDA: 20-800 **DATE:** January 24, 1997

DRUG:

INITIATED BY: __X__ APPLICANT __X__ FDA

SPONSOR: Bayer Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:

Bayer: Dr. Derrick Constable, Mr. Richard Costa, Mr. Ken Fleming, Dr. Bill Franhart, and Mr. David Mirabell

CDER/DPDP: Dr. Chong Ho Kim, Ms. Denise Toyer

TELEPHONE #: 509-482-1721

BACKGROUND

Reference is made to the Division's 1/24/97 facsimile requesting further CMC information for this NDA. This telecon was requested to clarify the Division's requests.

TELECON

David Mirabell started the telecon by stating the division's facsimile referred to the Division's minutes from the March 6, 1996 industry meeting with Bayer. They have never received a copy of these minutes. A copy will be provided immediately. The following questions were clarified for Bayer.

Question 3(b). There is no proposal for an expiration dating period of the drug product.

This was an oversight by Bayer, they will submit a proposal for an expiration period which corresponds to [redacted] expiration of the epinephrine [redacted] Dr. Kim explained that the proposal should be based on stability data. The process record requested in question 2 will supply [redacted] data. The sponsor does not anticipate any chemical, physical or other changes to the [redacted] because the physical attributes of the [redacted] will not be altered. Dr. Kim reiterated that although the [redacted] would not be altered the placement of the [redacted] in a different environment may affect the stability of the epinephrine and ultimately the expiration date. Once Dr. Kim receives the process record he will be able to comment further on this point.

Question 3(c). The proposed stability protocol is not acceptable...

Dr. Kim stated that the ICH guidelines for stability should be followed. The sponsor felt the ICH guidelines did not apply to this product because the guidelines are based on a solid dosage formulation. They don't expect the device to rust or to exhibit mechanical malfunction as a result of the repackaging. Bayer

will review the guidelines and make a proposal to the division regarding the stability protocol.

Question 3(d). The following stability time points are suggested

The sponsor wanted to know if a [redacted] stability time point is required. They feel sufficient data are available to support a [redacted] expiration. Therefore requiring a [redacted] time point will not provide additional data. Dr. Kim reminded the sponsor that epinephrine is not an extremely stable drug and there is concern about the degradation products. Once the process record from [redacted] has been submitted he will be able to comment further.

Question 4. What further information is required for the Environmental Assessment (EA).

Dr. Kim recommended that the sponsor contact Nancy Sager at CDER for further information of the EA. The project manager will provide the phone number.

Question 5. The Division requested further testing of the performance of the device through clothing. Does the Division have any required fabrics that it prefers?

Although the division does not have specific requirements for performance testing through clothing we would encourage the sponsor to conduct these tests using commonly used clothing, e.g. jean, cotton, etc. The sponsor may submit a protocol for review and comment.

/ST

Denise P. Toyer
Project Manager

cc: Orig. NDA 20-800
HFD-570/Division File
HFD-570/Toyer
HFD-570/Kim/1-27-97
HFD-570/Poochikian/1-29-97
HFD-570/Nicklas
HFD-570/Williams
N:\staff\toyerd\n20800.tel

Toyer

Memorandum of Telephone Facsimile Correspondence

Date: January 22, 1997

To: David L. Mirabell
Manager,
Regulatory Affairs

From: Denise P. Toyer
Project Manager

Through: Cathie Schumaker
Chief, Project Management Staff

Subject: NDA 20-800, Information Request

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

DT

Denise P. Toyer
Project Manager
Division of Pulmonary Drug Products

NDA 20-800

The following multi-disciplinary comments are in response to a preliminary review of NDA 20-800 which was submitted on December 6, 1996.

1. Please provide the listed reference product that the 505(b)2 application is based upon.

2. The following comments pertain to the stability protocol for Epinephrine Injection, U.S.P. 1:1000 manufactured by You should provide the following information:

   a. a copy of Process Record No.
   b. a copy of for testing; and
   c. the Degradation Products Profile, specifications and test methods. (The degradation products specifications should also contain individual limit and total limit.)

3. The following comments pertain to the stability of the drug product

   a. You stated that you will incorporate elevated stability studies of approximately in duration per our request (see our meeting minutes dated March 6, 1996 and your correspondence dated October 28, 1996). Stability data for the alone is provided. However, there are **NO** stability data for the Please provide the requisite data.

   b. There is no proposal for an expiration dating period of the drug product.

   c. The proposed stability protocol is not acceptable. The stability protocol should be modified to include 25°C/60%RH for long term stability and 40°C/75%RH for accelerated stability. We strongly suggest that you provide a modified stability protocol for our comments.

   d. The following stability time points are suggested

   e. Three points stability commitments should be provided.

4. The following comments pertain to the Environmental Assessment.

   The environmental impact statement provided is inadequate, e.g, an environmental assessment was provided for the applicator, however no environmental assessment regarding

the drug substance and/or constituents of the formulation were provided. You should provide a new version of the environmental assessment with appropriate information.

5. During the March 6, 1996 pre-NDA meeting the Division suggested testing the performance of the device when administered through clothing. These data were not found in the submission. Please provide these data or an explanation as to why you decided the study was not needed.

The filing date for this NDA is February 4, 1997, please respond to these comments as soon as possible. If you have any questions, please contact Ms. Denise Toyer, Project Manager, at (301) 827-1089.

cc:
Orig. NDA 20-800
HFD 570- KIM
HFD 570- WILLIAMS
HFD 570 -NICKLAS
HFD 570-TOYER
HFD 570 - DIVISION FILE

MESSAGE CONFIRMATION

01/23/97 09:36
ID=PULMONARY DIV FDA

ID.	MODE	BOX	GROUP
339	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
01/23 09:35	01'09"	509 484 4320	003/003	OK		0000

Memorandum of Telephone Facsimile Correspondence

Date: January 22, 1997

To: David L. Mirabell
Manager,
Regulatory Affairs

From: Denise P. Toyer
Project Manager

Through: Cathie Schumaker
Chief, Project Management Staff

Subject: NDA 20-800, Information Request

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Toyer

NDA 20-800

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

Attention: David L. Mirabell
Manager, Regulatory Affairs

Dear Mr. Mirabell:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	— (epinephrine, USP) Injection 1:1000
Therapeutic Classification:	Standard
Date of Application:	December 5, 1996
Date of Receipt:	December 6, 1996
Our Reference Number:	NDA 20-800

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 4, 1997 in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Ms. Denise Toyer, Project Manager, at (301) 827-1089.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/

Cathie Schumaker
Chief, Project Management Staff
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-800
HFD-570/Div. Files
HFD-570/Toyer
DISTRICT OFFICE

Drafted by: dpt/December 19, 1996
Final: pw/December 20, 1996

N:\STAFF TOYERD\n20800.let

ACKNOWLEDGMENT (AC)