020800_Original Approval_ Package.PDF

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-800

Trade Name:	Twinject Auto Injector
Generic Name:	Epinephrine injection USP 1:1000
Sponsor:	Hollister-Stier Laboratories, LLC
Approval Date:	June 6, 2003
Indications:	Provides for the use of Twinject for treatment of severe allergic reactions, including anaphylaxis and anaphylactoid reactions, in response to exposure to bee stings, allergy injections, etc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-800

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-800

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-800

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

Attention: David L. Mirabell
Director, Regulatory & Professional 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 Twinject Auto-Injector (epinephrine injection 1:1000).

We acknowledge receipt of your submissions dated January 10, and 27, and February 14, and 24, and April 3, 9, 18, and May 29, and September 5, and October 1, and November 10, and December 4, 1997, and 29, May, and June 17, and July 16, and August 24, 1998, and August 16, and December 13, 1999, and April 21, 2000, and March 29, and June 26, and July 17, and August 15, and September 28, and October 29, and December 19, 2001, and February 6, and June 1, and July 26, and August 15, and September 24, and 25, and November 4, and 18, and December 10, 2002, and January 29, and 31, March 31, and May 22, 28, and 29, 2003.

The May 22, 2003, submission constituted a complete response to our January 29, 2003, action letter.

This new drug application is indicated for treatment of severe allergic reactions, including anaphylaxis and anaphylactoid reactions, in response to exposure to bee stings, allergy injections, etc.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the (package insert submitted May 22, 2003, patient information leaflet submitted January 29, 2003, immediate container and carton labels submitted January 29, 2003). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 20-800**." Approval of this submission by FDA is not required before the labeling is used.

(b)(4)

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/Division of Pulmonary & Allergy Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
5/30/03 04:39:11 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-800

APPROVABLE LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-800

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

Attention: David L. Mirabell
Director, Regulatory Affairs & Professional Services

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 Twinject (epinephrine) Auto-Injector.

We acknowledge receipt of your submissions dated July 26, August 15, September 24, and 25, November 4, and 18, December 10, 2002, and January 29, 2003.

The July 26, 2002, submission constituted a complete response to our December 18, 2001, action letter.

We completed our review of this application, as submitted, with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to resolve the following deficiency. -

> During the recent inspection of the — manufacturing facility for your NDA, a number of deficiencies were noted. Satisfactory inspection will be required before this application may be approved.

In addition, you must submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the agreed upon labeling (package insert, patient package insert, immediate container and carton labels submitted January 29, 2003).

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiency, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary & Allergy Drug Products and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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.

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, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-1084.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Acting Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Marianne Mann
1/29/03 03:41:54 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-800

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

Attention: David L. Mirabell
Director, Regulatory Affairs and Professional Services

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 Twinject (epinephrine) 1:1000 Injection.

We acknowledge receipt of your submissions dated June 26, July 17, August 15, September 28, and October 29, 2001. Your submission of June 26, 2001, constituted a complete response to our September 14, 2000, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. The following comments pertain to the specifications and test methods for the ———

   a. Tighten the acceptance criteria for ———, total known impurities, and total impurities based on the batch analysis data submitted.

   b. Assign a specific test method number for each test. Inclusion of several test methods in a SOP (e.g., SOP ——, is not acceptable. Adopt a unique identification number for each test that will allow traceability of each subsequent modification.

   c. Tighten the bulk release test limit for sodium bisulfite. ——— ——— of target).

   d. Revise the ——— Release Criteria (by Abbott Lab) so that it is tighter or equal to those of Acceptance Criteria by the Hollister-Stier Lab, as described below, and modify the release criteria and the acceptance criteria.

      (1) ——— (NMT —— vs NMT ———

      (2) Total Known Impurities (NMT —— vs NMT ——)

(3) Total Impurities (NMT [redacted] vs NMT [redacted]

e. Propose an upper limit for "Fill Volume".

f. Provide specification sheets with test methods to reflect the above modifications.

2. The following comments pertain to the needle assembly.

a. You have provided Twinject samples c[redacted]color hub and [redacted]olor sheath. However, the drawing of the needle assembly on page 1095, vol. 1.3 in the amendment dated June 26, 2001, is for [redacted] color hub and [redacted] color sheath. Provide a drawing of the actual sample with legible markings of the unit.

b. Provide acceptance criteria and test methods of the needle assembly.

3. The following comments pertain to the [redacted] stability protocol.

a. Identify the attributes that are monitored at various time-points. Provide a new protocol in a tabular format.

b. Assign a specific test method for each test. See comment 1(b) above.

c. The acceptance criteria for sodium bisulfite ([redacted] at release; NLT [redacted], at [redacted] for shelf life) and chlorobutanol ([redacted] at release) are not acceptable. Provide data to demonstrate the preservative effectiveness outside the proposed extremes.

d. Tighten the specific limits for the epinephrine degradation products and impurities, e.g., [redacted] (NMT [redacted] for release & NMT [redacted] for shelf life); [redacted] (NMT [redacted] for shelf life); Total Known Impurities (NMT [redacted] for release & NMT [redacted] for shelf life); Total Impurities (NMT [redacted] for release & NMT [redacted] for shelf life).

e. Provide updated stability data. Comments on the proposed expiry of [redacted] will be deferred pending receipt and evaluation of updated data.

4. The following comments pertain to the assembled Twinject™ Auto-Injector.

a. Revise the product name in all documents to reflect the new name, Twinject Auto-Injector. Delete all other names (e.g., [redacted] etc).

b. Identify each manufacturer's responsibility (e.g., manufacture, release test, stability, etc.) in a tabular format.

5. The analytical method for the rubber extractables study is not sensitive. Improve the sensitivity

of the method.

6. The following comments pertain to the Twinject™ stability protocol/ summary report.

a. The stability protocol for Twinject™ Epinephrine Auto-Injectors (Table 5C) is inadequate. As we commented earlier (Comment 8, letter dated February 15, 2000), the stability protocol should contain tests, method numbers, and appropriate stability commitments. Revise the stability protocol and submit a comprehensive stability protocol. Address the following comments in your revised stability protocol:

(1) Include at least two different storage conditions, e.g., room temperature condition and accelerated condition.

(2) Provide appropriate acceptance criteria for sodium bisulfite and for chlorobutanol.

(3) Provide firm sterility test time-points, e.g., at [redacted] for this drug product.

(4) Include appropriate performance test attributes.

(5) Address comments 3(a)–3(d) on the [redacted] stability protocol for the Twinject stability protocol, also.

b. The stability report in Table 5A, (amendment dated October 29, 2001), does not provide adequate and comprehensive data per stability protocol submitted in Vol. 1.4, page 1214, amendment dated June 26, 2001. Include in the stability report acceptance criteria for each attribute. Provide adequate stability data on samples stored under all stability storage conditions.

c. The submitted [redacted] stability data in Table 5A, (amendment dated October 29, 2001), show the following observations. Explain these observations with supportive data, and introduce appropriate modifications in the manufacturing, analytical procedures, etc.

(1) Initial values of sodium bisulfite level are [redacted] of the target [redacted]

(2) Slight increase in sodium bisulfite levels were observed within [redacted]

(3) Initial values of chlorobutanol are [redacted] of the target [redacted]

(4) Slight increase in the chlorobutanol levels were observed in [redacted]

7. Comments 1(a)–1(f) above concerning the [redacted] are equally applicable to the specifications and test methods for Twinject™. Introduce all the modifications and provide

appropriate documentation.

8. The following comments pertain to the microbiology issues.

   a. Provide information regarding the validation of the [redacted] sterilization process for the sterile needles. Include information such as bioburden, dosimeter locations, and results from validation runs.

   b. Perform endotoxin testing of the product as a part of the stability program. Testing should, at a minimum, take place at expiry.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required. Submit revised draft labeling identical in content to the enclosed labeling (text for the package insert, text for the patient package insert), and as listed below for the container label.

[redacted]

In addition, when you respond to the above deficiencies, include a safety update as described in 21CFR 314.50(d)(5)(vi)(*b*). You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

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 314.110. 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 meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

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, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-5584.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:

471330-H01

9 Draft Labeling Page(s) Withheld

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

/s/

Marianne Mann
12/18/01 08:42:33 AM
M.Mann signing as Acting Director for Dr. Robert Meyer

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 20-800

Food and Drug Administration
Rockville MD 20857

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

FEB 17 2000

Attention: David L. 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 Twinject (epinephrine) 1:1000 Injection.

We acknowledge receipt of your submissions dated August 16, and December 13, 1999. Your submission of August 16, 1999, constituted a complete response to our November 9, 1998, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to adequately address the following.

* (Note: Alphanumeric designations appearing in parentheses following the comments below refer to the comments of the November 9, 1998, Agency letter.)

1. The proposed acceptance specifications for the [redacted] are unacceptable. Tighten all your proposed "incoming"/release and shelf-life specifications. The acceptance specifications should be generated with fresh or less than 3 months old samples. (Comment 1.c.)

2. Tighten the proposed acceptance criterion for the [redacted] test to be more reflective of the observed data. (See page 13 of your submission dated August 16, 1999, and comment 8.d. below.) Provide data to relate the proposed standard to a known [redacted] standard, e.g., [redacted] (Comment 1.e.)

3. Drug master file (DMF) [redacted] for the [redacted] is deficient and the DMF holder has been notified in a letter dated January 18, 2000. (Comment 2)

4. Tighten the pH specifications as follows:

   Release: —

   Shelf-life: —

   Alternatively, you can justify your proposed shelf-life pH limit by demonstrating quantitative impurity profiles at the extreme pH levels. (Comment 3.a.)

5. Reduce the proposed break-loose force to, e.g., — (Data provided on page 22 of the submission dated August 16, 1999, show that the gross mean is — and the highest mean of a batch is —) (Comment 3.b.)

6. Tighten the proposed acceptance criteria for dose delivery time to NMT — for the mean and NMT — for individual units. (Comment 3.f.)

7. The following comments pertain to the firing force. (Comment 3.g.)

   a. Explain your statement that "although — design has been changed, old validation data of — are still applicable."

   b. Tighten the proposed acceptance criteria for activation force to e.g., mean of — , and individual ranges from — .

8. The following comments pertain to the stability protocol. (Comment 5)

   a. Submit a stability protocol that contains sampling plan, specifications, and withdrawal commitment. Refer to comment 8 in the Agency's letter dated December 4, 1997.

   b. Tighten the pH limit to — (See comment 4 above.)

   c. Justify the proposed sodium bisulfite limit NLT — through stability studies.

   d. Reduce the proposed expiration dating period from the date of the manufacture of — to —

9. Update specifications and test methods for release and stability to reflect all the modifications.

10. Provide a study evaluating the time necessary for patients with disabilities, such as debilitating arthritis, in performing the steps necessary for preparing the second dose of epinephrine. If a study is not conducted, the label may indicate that the product is not suitable for patients with such disabilities.

11. The following are preliminary comments on the labeling. Modify and submit the draft package insert and carton and container labels to reflect the comments and the revisions listed below. Further labeling comments will be provided once the deficiencies noted below are adequately addressed.

    a. Throughout the package insert, carton, and container labels, the statement "[redacted]" should read "Each 0.3 mL of Epinephrine Injection, USP (1:1000) contains 0.3 mg *l*-epinephrine".

    b. On the container label, "[redacted] should read "[redacted]

    c. The font size and prominence of "(epinephrine) USP 1:1000" should be half that of Twinject™. The word "Injection" should follow "epinephrine".

    d. "Manufactured by" should read "Manufactured for".

    e. The pregnancy category C section of the labeling should read "Epinephrine has been shown to have developmental effects in rabbits at a subcutaneous dose of 1.2 mg/kg (approximately 33 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis), in mice at a subcutaneous dose of 1 mg/kg (approximately 7 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis), and in hamsters at a subcutaneous dose of 0.5 mg/kg (approximately 9 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis). These effects were not seen in mice at a subcutaneous dose of 0.5 mg/kg (approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis)."

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

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

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 314.110. 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 meeting or teleconference with the Division of Pulmonary and Allergy Drug Products to discuss what further steps need to be taken before the application may be approved.

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, call Ms. Ladan Jafari, Project Manager, at (301) 827-5584.

Sincerely,

/S/

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 20-800

Food and Drug Administration
Rockville MD 20857

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

SEP 14 2000

Attention: David L. Mirabell
Director, Regulatory Affairs and Professional Services

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 Twinject (epinephrine) 1:1000 Injection.

We acknowledge receipt of your submission dated April 21, 2000. This submission constituted a complete response to our February 17, 2000, action letter.

We have completed the 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). Before this application may be approved, it will be necessary for you to address the following. The comment numbers in parenthesis following the comments below refer to the comments from the February 17, 2000, Agency letter.

1. The following comments pertain to the acceptance criteria for [redacted] and shelf-life specifications for epinephrine degradants in the products. (Comment 1)

   a. Tighten the incoming limit and the shelf-life limit for [redacted] to [redacted] respectively.

   b. Tighten the incoming limit and the shelf-life limit for [redacted] to [redacted] respectively.

   c. Tighten the incoming limit and the shelf-life limit for [redacted] to [redacted] each.

   d. Tighten the incoming limit and the shelf-life limit for [redacted] to [redacted] respectively.

   e. Provide data on [redacted] level in the drug product at various time points.

   f. Tighten the proposed incoming limit and the shelf-life limit for total known impurities to [redacted] respectively.

g. Tighten the proposed incoming limit and the shelf-life limit for total impurities to [redacted] respectively.

2. Tighten the [redacted] shelf-life specifications (e.g., NMT [redacted]. (Comment 2)

3. Tighten the dose delivery time to NMT [redacted] for the mean and NMT [redacted] for the individual unit. The release criteria should be the same as the shelf-life for dose delivery time. (Comment 6)

4. The following comments pertain to the firing force. (Comment 7)

   a. Provide detail information for the firing force test method and specifications. Specify the number of units to be tested.

   b. Provide raw data from which the Table B on Page 18 (Summary of Stability Data) was derived. Additionally, provide standard deviation for each test point.

   c. Reduce the acceptance criteria range significantly.

5. The following comments pertain to the stability protocol.

   a. Modify the number of batches to put on the stability to "the first three production batches and a reasonable portion of the annual production batches thereafter." (Comment 8.a.)

   b. To justify your proposed sodium bisulfite limit of NLT [redacted], provide stability data up to [redacted] on the levels of sodium bisulfite and epinephrine in the drug product. (Comment 8.c.)

   c. Reduce the expiration dating period to [redacted] Expiration dating period should be initiated from the date of the [redacted] manufacture. (Comment 8.d.)

   d. Update the stability protocol to reflect the above information.

6. Update the specifications and test methods for release and stability to reflect all the modifications made. (Comment 9)

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

Labeling comments will be provided when the above issues have been addressed.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

You are advised to contact the Division regarding the extent and format of your safety update prior to responding to this letter.

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 314.110. 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 meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

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, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-5584.

Sincerely.

/S/

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research