CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

019430Orig1s015

Trade Name: EpiPen and EpiPen Jr. Auto Injector

Generic or Proper Name: epinephrine injection, USP

Sponsor: Meridian Medical Technologies

Approval Date: 04/16/2002

Indication: EpiPen and EpiPen Jr. contain epinephrine, a non-selective alpha and beta-adrenergic receptor agonist, indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis.

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APPLICATION NUMBER:

019430Orig1s015

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019430Orig1s015

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-430/S-015

Meridian Medical Technologies
2550 Hermelin Drive
St. Louis, MO 63144-2591

Attention: Thomas Freund
Manager, Regulatory Affairs

Dear Mr. Freund:

Please refer to your supplemental new drug application dated November 21, 2001, received November 23, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for EpiPen and EpiPen Jr. Auto Injector.

This "Changes Being Effected in 30 days" supplemental new drug application proposes to reduce the shelf life of the EpiPen Auto Injector from 27 to 20 months and change the stability protocols for the EpiPen and EpiPen Jr. Auto Injectors.

We have completed the review of this supplemental application, and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 8271084.

Sincerely,

{See appended electronic signature page}

Guirag Poochikian, Ph.D.
Chemistry Team Leader,
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC II, Office of New Drug Chemistry
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/

Guiragos Poochikian

4/16/02 11:46:30 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019430Orig1s015

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW *Review #1*	1. ORGANIZATION HFD-570 DPADP	2. NDA NUMBER 19-430
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Meridian Medical Technologies, Inc. 2550 Hermelin Drive St. Louis, MO 63144		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S) SCE-015(11/21/01)
6. NAME OF DRUG EpiPen Auto-Injector	7. NONPROPRIETARY NAME Epinephrine Injection	
8. SUPPLEMENT PROVIDES FOR: To reduce the shelf life of the EpiPen auto-injector from 27 to 20 months and change the stability protocols for the EpiPen and EpiPen Junior Auto-injectors.		
9. PHARMACOLOGICAL CATEGORY Adrenergic. To be used to treat anaphylaxis.	10. HOW DISPENSED RX x OTC ___	11. RELATED IND/NDA/DMF
12. DOSAGE FORM(S) Injection	13. POTENCY 0.3 mg/0.3 mL & 0.15 mg/0.3 mL	
14. CHEMICAL NAME AND STRUCTURE See USAN Dictionary.		15. RECORDS AND REPORTS CURRENT YES___NO REVIEWED YES___NO

16. COMMENTS:
cc:
Orig. NDA #19-430
HFD-570/Div. File
HFD-570/CHKim/
HFD-570/GPoochikian
HFD-570/RNicklas
HFD-570/LJafari
R/D Init. By:_____
F/T by: CHKim/
Doc #N19-430cbe.s15.doc

17. CONCLUSIONS AND RECOMMENDATIONS

Chemist recommends the supplement to be approved.

18. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Chong-Ho Kim, Ph.D.		April 9, 2002

Background

FP-S-X
FP-S-T

MASTER STABILITY PROTOCOL

Page 1 of 5

EpiPen® AUTO-INJECTOR
1:1000 EPINEPHRINE INJECTION,
0.3 mg/0.3 mL DOSE

Supersedes Date: 11/20/98

Effective Date: NOV 15 2001

1.0 GENERAL PRODUCT INFORMATION

1.1 Composition

The EpiPen Auto-injector shall deliver 0.3 mg per 0.3 mL of Epinephrine Injection. The drug product shall be composed of the following formulation:

Ingredients	Unit Formula
Epinephrine, USP	(b) (4) *
Sodium Chloride, (b) (4)	6.00 mg/mL
Sodium Metabisulfite, (b) (4)	1.67 mg/mL
Water for Injection, (b) (4)	(b) (4)
Hydrochloric Acid, (b) (4)	(b) (4)
(b) (4)	(b) (4)

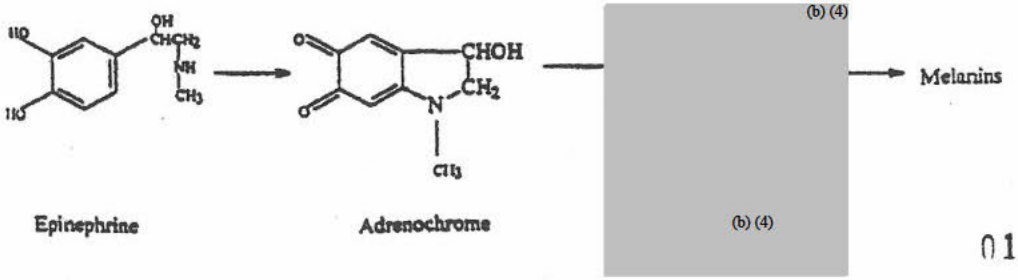
* **Includes (b) (4). Amount to be calculated based on the potency of the Control Number used.**

1.2 Container/Closure

The immediate container/closure system consists of a (b) (4) contains the drug product. The components utilized are listed below:

(b) (4)

1.3 Degradation Pathway and Degradation Products



Epinephrine Adrenochrome

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FP-S-X
FP-S-T

MASTER STABILITY PROTOCOL

Page 2 of 5

EpiPen® AUTO-INJECTOR
1:1000 EPINEPHRINE INJECTION,
0.3 mg/0.3 mL DOSE

Supersedes Date: 11/20/98

Effective Date: NOV 15 2001

2.0 TEST METHODS AND SPECIFICATIONS

2.1 Analytical Tests (25 units)

Test	Method	Limits
Epinephrine Assay - Adrenochrome - (b) (4) - Total Other Impurities - Total Impurities	(b) (4)	(b) (4)
Sodium Metabisulfite Assay		
pH	(b) (4)	2.2 - 5.0
Color and Clarity		Conforms: Lacks precipitate and/or pink discoloration; degree of yellow color development does not exceed standard.

2.2 Microbiological Tests

Test	Units Tested	Method	Limits
Bacterial Endotoxin	10	(b) (4)	(b) (4)
Sterility	40		

2.3 Physical Tests (13 units)

Test	Method	Limits
Particulate Matter	(b) (4)	(b) (4)

2.4 **Functional Tests (25 units)**

Test	Method	Limits
Activation Force	(b) (4)	(b) (4)
Volume Dispensed		
Dispensing Time		
Exposed Needle Length		

3.0 STUDY DESIGN

3.1 Commitment/Stability Batch Production

3.1.1 Any significant change in the manufacturing process may require the first three production lots incorporating such changes to be placed on stability.

3.1.2 The first three production batches of the product are designated for long term stability studies following any significant changes. Stability units will be sampled representatively from each batch as final packaging is taking place. Refer to Section 4 for the Study Plan.

3.1.3 Following the first three production batches, one batch of each presentation will be placed on stability per year, providing manufacturing occurs within the year. Refer to Section 4 for the Study Plan.

3.1.4 Ongoing stability data will be submitted to the FDA as part of the annual Periodic Report.

3.1.5 In all instances Meridian Medical Technologies agrees to promptly withdraw from the market any production batches which do not meet specifications and will notify the FDA. As an alternative to market withdrawal, Meridian Medical Technologies may immediately discuss the failure to meet specifications with the appropriate reviewing divisions of the FDA and provide justification for the continued distribution of that batch.

3.2 Storage and Sampling

The first three batches manufactured will be placed in the stability program as outlined in Section 4 following any significant change. Thereafter, one production batch per presentation per year will be placed into the program. Random samples will be removed at specified intervals and submitted for the required testing. The real time stability data will be utilized to support the established product expiration date.

Long term stability studies will be performed on units stored at 25°C ± 2°C, 60% RH ± 5% RH.

Units will be stored in a horizontal position to simulate drug contact with components equivalent to normal storage.

At each test interval, representative samples will be randomly removed and submitted for the appropriate testing.

4.0 STUDY PLAN

The stability profile will include testing for physical, chemical, functional and microbiological attributes. Analytical testing will include quantitation of degradation products and antioxidant assay.

4.1 Storage and Sampling Plan

TIME (MONTHS)

CONDITIONS:	0	3	6	12	18	20	24	27
25° C ± 2° C, 60% RH ± 5% RH	A	C	C	B	C	A	C	C

Minimum number of units required:	414
Minimum required x 1.2:	497
Sample size to be requested (rounded up in units of 12):	504

4.2 Sample Code Designation

Code	Tests - Analytical	Test - Functional
A (113 units)	Epinephrine Assay Sodium Metabisulfite pH Degradation Products Color & Clarity	Activation Force Delivered Volume Dispensing Time Exposed Needle Length
	Tests - Microbiological	Test - Physical
	Sterility Bacterial Endotoxin Content	Particulate Matter

APPEARS THIS WAY ON ORIGINAL

FP-R-X
FP-J-T

MASTER STABILITY PROTOCOL

Page 1 of 5

EpiPen® Jr. AUTO-INJECTOR
1:2000 EPINEPHRINE INJECTION,
0.15 mg/0.3 mL DOSE

Supersedes Date: 11/20/98

Effective Date: NOV 15 2001

1.0 GENERAL PRODUCT INFORMATION

1.1 Composition

The EpiPen Jr. Auto-injector shall deliver 0.15 mg per 0.3 mL of Epinephrine Injection. The drug product shall be composed of the following formulation:

Ingredients	Unit Formula
Epinephrine, USP	(b) (4) *
Sodium Chloride, (b) (4)	6.00 mg/mL
Sodium Metabisulfite, (b) (4)	1.67 mg/mL
Water for Injection, (b) (4)	(b) (4)
Hydrochloric Acid, (b) (4)	
(b) (4)	

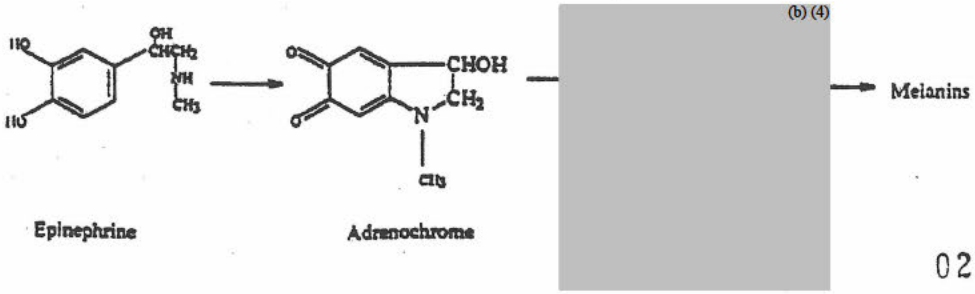
* **Includes** (b) (4) **Amount to be calculated based on the potency of the Control Number used.**

1.2 Container/Closure

The immediate container/closure system consists of a (b) (4) contains the drug product. The components utilized are listed below:

(b) (4)

1.3 Degradation Pathway and Degradation Products



Epinephrine Adrenochrome

FP-R-X
FP-J-T

MASTER STABILITY PROTOCOL

Page 2 of 5

EpiPen® Jr. AUTO-INJECTOR
1:2000 EPINEPHRINE INJECTION,
0.15 mg/0.3 mL DOSE

Supersedes Date: 11/20/98

Effective Date: NOV 1 5 2001

2.0 TEST METHODS AND SPECIFICATIONS

2.1 Analytical Tests (25 units)

Test	Method	Limits
Epinephrine Assay - Adrenochrome - (b) (4) - Total Other Impurities - Total Impurities	(b) (4)	(b) (4)
Sodium Metabisulfite Assay		
pH	(b) (4)	2.2 - 5.0
Color and Clarity		Conforms: Lacks precipitate and/or pink discoloration; degree of yellow color development does not exceed standard.

2.2 Microbiological Tests

Test	Units Tested	Method	Limits
Bacterial Endotoxin	10	(b) (4)	(b) (4)
Sterility	40		

2.3 Physical Tests (13 units)

Test	Method	Limits
Particulate Matter	(b) (4)	(b) (4)

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2.4 Functional Tests (25 units)

Test	Method	Limits
Activation Force	(b) (4)	(b) (4)
Volume Dispensed		
Dispensing Time		
Exposed Needle Length		

3.0 STUDY DESIGN

3.1 Commitment/Stability Batch Production

3.1.1 Any significant change in the manufacturing process may require the first three production lots incorporating such changes to be placed on stability.

3.1.2 The first three production batches of the product are designated for long term stability studies following any significant changes. Stability units will be sampled representatively from each batch as final packaging is taking place. Refer to Section 4 for the Study Plan.

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3.1.4 Ongoing stability data will be submitted to the FDA as part of the annual Periodic Report.

3.1.5 In all instances Meridian Medical Technologies agrees to promptly withdraw from the market any production batches which do not meet specifications and will notify the FDA. As an alternative to market withdrawal, Meridian Medical Technologies may immediately discuss the failure to meet specifications with the appropriate reviewing divisions of the FDA and provide justification for the continued distribution of that batch.

3.2 Storage and Sampling

The first three batches manufactured will be placed in the stability program as outlined in Section 4 following any significant changes. Thereafter, one production batch per presentation per year will be placed into the program. Random samples will be removed at specified intervals and submitted for the required testing. The real time stability data will be utilized to support the established product expiration date.

Long term stability studies will be performed on units stored at 25°C ± 2°C, 60% RH ± 5% RH.

Units will be stored in a horizontal position to simulate drug contact with components equivalent to normal storage.

At each test interval, representative samples will be randomly removed and submitted for the appropriate testing.

4.0 STUDY PLAN

The stability profile will include testing for physical, chemical, functional and microbiological attributes. Analytical testing will include quantitation of degradation products and antioxidant assay.

4.1 Storage and Sampling Plan

TIME (MONTHS)

CONDITIONS:	0	3	6	12	18	20	24
25° C ± 2° C, 60% RH ± 5% RH	A	C	C	B	C	A	C

Minimum number of units required:	389
Minimum required x 1.2:	467
Sample size to be requested (rounded up in units of 12):	468

4.2 Sample Code Designation

Code	Tests - Analytical	Test - Functional
A (113 units)	Epinephrine Assay	Activation Force
	Sodium Metabisulfite	Delivered Volume
	pH	Dispensing Time
	Degradation Products	Exposed Needle Length
	Color & Clarity	
	Tests - Microbiological	Test - Physical
	Sterility	Particulate Matter
	Bacterial Endotoxin Content	

FP-R-X
FP-J-T

MASTER STABILITY PROTOCOL

Page 5 of 5

EpiPen® Jr. AUTO-INJECTOR
1:2000 EPINEPHRINE INJECTION,
0.15 mg/0.3 mL DOSE

Supersedes Date: 11/20/98

Effective Date: NOV 1 5 2001

Code	Tests - Analytical	Test - Functional
B (63 units)	Epinephrine Assay Sodium Metabisulfite pH Degradation Products Color & Clarity	Activation Force Delivered Volume Dispensing Time Exposed Needle Length
	Test - Physical Particulate Matter	

Code	Tests - Analytical
C (25 units)	Epinephrine Assay Sodium Metabisulfite pH Degradation Products Color & Clarity

5.0 DATA ANALYSIS AND REPORTING

5.1 Data collected from the testing of samples stored at 25°C will be analyzed to confirm product expiration date. Shelf life is interpreted as the time value at which the 95% confidence limit for the mean degradation curve intersects the acceptable lower (or upper) specification limit for samples held at 25°C.

5.2 Amendments to this protocol must be documented and be approved by Research and Development, Regulatory Affairs and Quality. Also, FDA will be notified of all amendments to the protocol. As part of their approval, Regulatory Affairs will determine the appropriate method of FDA notification.

Written By / Date: 11/13/01

APPROVALS / DATE:

Quality	Clint Frazer 11-13-01
Research and Development	11/13/01

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/s/

Chong-Ho Kim
4/16/02 10:06:18 AM
CHEMIST

Guiragos Poochikian
4/16/02 11:43:49 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019430Orig1s015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-430/S-015

CBE-30 SUPPLEMENT

Meridian Medical Technologies, Inc.
2550 Hermelin Drive
St. Louis, MO 63144

Attention: Thomas G. Freund
Manager, Regulatory Affairs

Dear Mr. Freund:

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

Name of Drug Product: EpiPen and EpiPen Jr. Auto-Injectors

NDA Number: 19-430

Supplement Number: S-015

Date of Supplements: November 21, 2001

Date of Receipt: November 23, 2001

This supplemental application submitted as "Supplement - Changes Being Effected in 30 days" supplement proposes to reduce the shelf life of the EpiPen AutoInjector from 27 to 20 months and change the stability protocols for the EpiPen and EpiPen Junior AutoInjectors.

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on January 23, 2002, in accordance with 21 CFR 314.101(a). If the applications are filed, the user fee goal date will be May 23, 2002.

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

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

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

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
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/

Ladan Jafari
11/29/01 03:24:48 PM
Signed for Sandy Barnes.