

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201739Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 201739	NDA Supplement #: S- 00	Efficacy Supplement Type SE-
Proprietary Name: Auvi-Q Established/Proper Name: Epinephrine Injection USP 1:1000 Dosage Form: Auto-Injector Strengths: 0.15 mg and 0.3 mg		
Applicant: Intelliject Inc.		
Date of Receipt: May 7, 2012		
PDUFA Goal Date: November 7, 2012		Action Goal Date (if different):
Proposed Indication(s): Emergency Treatment of allergic reactions		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. (*If not clearly identified by the applicant, this information can usually be derived from annotated labeling.*)

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
EpiPen, NDA 019430	Safety and efficacy

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

BA studies

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If “YES,” list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
EpiPen	019430	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application: EpiPen

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for combination product using a new device.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

While duplicate drug product is available with other devices, the device is new; therefore, the application was not eligible for submission under 505(j) per OGD.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 7449012, 8048035 and 7794432

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s): *7449012, 8048035 and 7,794,432*
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *March 14, 2012 and December 9, 2010*

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

Applicant was sued for the '432 patent and not sued for the '012 and '035 patents. Patent infringement suit for the '432 was dismissed by a Delaware District Court on 2/16/12.

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/s/

ANGELA H RAMSEY
08/07/2012

505(b)(2) ASSESSMENT

Application Information		
NDA # 201739	NDA Supplement #: S- 00	Efficacy Supplement Type SE-
Proprietary Name: e-cue Established/Proper Name: Epinephrine Injection USP 1:1000 Dosage Form: Auto-Injector Strengths: 0.15 mg and 0.3 mg		
Applicant: Intelliject Inc.		
Date of Receipt: September 29, 2010		
PDUFA Goal Date: July 29, 2011		Action Goal Date (if different):
Proposed Indication(s): Emergency Treatment of allergic reactions		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
EpiPen, NDA 019430	Safety and efficacy

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

BA studies

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If “YES,” list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
EpiPen	019430	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application: EpiPen

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for combination product using a new device.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

While duplicate drug product is available with other devices, the device is new; therefore, the application was not eligible for submission under 505(j) per OGD.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 7,449,012 and 7,794,432

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s): *7,449,012 and 7,794,432*
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *December 9, 2010*

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

ANGELA H RAMSEY
07/20/2011

Division of Pulmonary, Allergy, and Rheumatology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 201739

Name of Drug: Epinephrine EAI

Applicant: Intelliject Inc.

Labeling Reviewed

Submission Date: September 29, 2010

Receipt Date: September 29, 2010

Background and Summary Description

Intelliject submitted this proposed PLR labeling in a new 505(b) (2) application on September 29, 2010, received on September 29, 2010 for epinephrine auto-injector for the emergency treatment of allergic reactions.

Review

The proposed labeling submitted on September 29, 2010 was compared to the PLR labeling tool. There were no format deficiencies identified.

Recommendations

I recommend approval of the proposed labeling pending labeling negotiations between Intelliject and the review team.

Angela Ramsey

June 29, 2011

Regulatory Project Manager

Date

Sandy Barnes

July 13, 2011

Chief, Project Management Staff

Date

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

/s/

ANGELA H RAMSEY
07/19/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 17, 2011

To: Angela Ramsey, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Matt Falter, Regulatory Review Officer (DTC)
Roberta Szydlo, Regulatory Review Officer (Professional)
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Robyn Tyler, DTC Group Leader
Michael Wade, Regulatory Health Project Manager
(DDMAC)

Subject: NDA 201739
DDMAC draft labeling comments for Epinephrine Auto-Injector

DDMAC has reviewed the proposed product package insert (PI), proposed patient package insert (PPI), and proposed Instructions for Use (IFU) for NDA 201739 submitted for consult on June 7, 2011.

DDMAC's comments are based on the following versions of labeling sent via email from DPARP to DDMAC on June 7, 2011:

- **PI:** "11_04_26 201739 epinephrine PI marked.doc"
- **PPI and IFU:** "11 0606 NDA 201739 epinephrine PPI (marked).doc"
- **Trainer IFU:** "11 0606 NDA 201739 epinephrine trainer IFU (marked.).doc"

DDMAC does not have any comments at this time on the proposed IFU for the trainer device. Our comments on the PI, PPI, and IFU for NDA 201739 are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions regarding the PI please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov. If you have any questions regarding the PPI or IFUs, please contact Matt Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MATTHEW J FALTER
06/17/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

PATIENT LABELING REVIEW

Date: June 6, 2011

To: Badrul Chowdhury, M.D., Director
**Division of Pulmonary, Allergy and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

Melissa Hulett, MSBA, RN, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Twanda Scales, RN, MSN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package
Insert and Instructions for Use)

Drug Name: TRADENAME Auto-injector (epinephrine)

Dosage Form and
Route: For injection

Application
Type/Number: NDA 201739

Applicant: Intelliject, Inc.

OSE RCM #: 2010-2319

1 INTRODUCTION

On September 29, 2010 Intelliject Inc. (Intelliject) submitted a New Drug Application (NDA) for Epinephrine Auto-Injector (EAI). EAI is a compact, patient –actuated, auto-injection system that delivers epinephrine injection for the emergency treatment of allergic reactions (Type 1).

This review is written in response to a request by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TRADENAME (epinephrine). DRISK conferred with DMEPA and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft TRADENAME (epinephrine) Patient Package Insert (PPI) and Instructions for Use (IFU) received on September 29, 2010 and sent to DRISK on May 23, 2011.
- Draft TRADENAME (epinephrine) Trainer Instructions for Use (IFU) received on September 29, 2010 and sent to DRISK on May 23, 2011.
- Draft TRADENAME (epinephrine) Prescribing Information (PI) received September 29, 2010 and revised by the Review Division throughout the current review cycle and received by DRISK on May 23, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PP and IFU document using the Verdana font.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the prescribing information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the PPI and IFU are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI or the IFU.

Please let us know if you have any questions.

36 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

TWANDA D SCALES
06/06/2011

LASHAWN M GRIFFITHS
06/06/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 201739 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b)(4) (proposed) Established/Proper Name: Epinephrine Dosage Form: Auto-Inject Strengths: 0.15 mg and 0.3 mg		
Applicant: Intelliject Inc. Agent for Applicant (if applicable): Joy Vander Wal, Senior Director, Regulatory Affairs, RRD International, LLC		
Date of Application: September 29, 2010 Date of Receipt: September 29, 2010 Date clock started after UN:		
PDUFA Goal Date: July 29, 2011	Action Goal Date (if different):	
Filing Date: November 28, 2010	Date of Filing Meeting: November 4, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Emergency Treatment of allergic reactions		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 76,367				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			
Are all classification properties [e.g., orphan drug, OTC, 505(b)(2)] entered into tracking system? <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		✓		
<i>If yes, explain in comment column.</i>				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			

<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			✓		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].			✓		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?			✓		
<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			✓		
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			✓		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?					
<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>					

Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		✓		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		✓		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>		✓		

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).			✓	
Index: Does the submission contain an accurate comprehensive index?	✓			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	✓			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	✓			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	✓			
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&C Act</i>				

section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	✓			

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			✓	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		✓		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			✓	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			✓	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>			✓	
<p>BPCA (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>		✓		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	✓			
REMS	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i></p>		✓		
Prescription Labeling	<input type="checkbox"/> Not applicable			
<p>Check all types of labeling submitted.</p>	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
<p>Is Electronic Content of Labeling (COL) submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p>	✓			
<p>Is the PI submitted in PLR format?⁴</p>	✓			
<p>If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?</p>				

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	✓			
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	✓ OC CDRH			October 29, 2010 November 1, 2010
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s):				
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s) Date(s): September 25, 2009	✓			
<i>If yes, distribute minutes before filing meeting</i>				

<p>Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i></p>		✓		
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ATTACHMENT

MEMO OF FILING MEETING

DATE: November 4, 2010

BLA/NDA/Supp #: 201739

PROPRIETARY NAME: Proposed (b) (4)

ESTABLISHED/PROPER NAME: epinephrine auto-injection

DOSAGE FORM/STRENGTH: 0.15 mg and 0.3 mg Auto-Injector

APPLICANT: Intelliject Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Emergency Treatment of Allergic Reactions

BACKGROUND: Intelliject submitted a New Drug Application for Epinephrine Auto-Injector for emergency treatment of allergic reaction including anaphylaxis to allergens, idiopathic anaphylaxis or exercised induced anaphylaxis.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Angela Ramsey	Yes
	CPMS/TL:	Sandy Barnes	No
Cross-Discipline Team Leader (CDTL)	Susan Limb		Yes
Clinical	Reviewer:	Brian Porter	
	TL:	Susan Limb	Yes
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

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Clinical Pharmacology	Reviewer:	Liang Zhao	Yes
	TL:	Yun Xu	Yes
Biostatistics	Reviewer:	Feng Zhou	Yes
	TL:	Joan Buenconsejo	Yes
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kathy Young	Yes
	TL:	Molly Topper	Yes
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Ying Wang	Yes
	TL:	Prasad Peri	Yes
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Carolyn Volpe		Yes
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Badrul Chowdhury, M.D., Ph.D., Division Director	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review and chemical classifications and other properties [e.g., orphan drug, OTC, 505(b)(2)], are entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)

<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

ANGELA H RAMSEY
06/03/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: April 28, 2011

Application Type/Number: NDA 201739

To: Badrul Chowdhury, Division Director
Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

Through: Kellie Taylor, PharmD, Associate Director
Todd Bridges, RPh, Acting Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Colleen E. Brennan, RPh, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Labeling Review

Drug Name(s): (b) (4)
(epinephrine injection, USP)

Strength: 0.3 mg/0.3 mL and 0.15 mg/0.15 mL

Applicant/sponsor: Intelliject, Inc.

OSE RCM #: 2010-2318

***** Note: This review contains proprietary and confidential information that should not be released to the public. *****

1 INTRODUCTION

This review evaluates the proposed labels and labeling for (b) (4) (epinephrine injection, USP) auto-injector (NDA 201739) for areas of vulnerabilities that could lead to medication errors.

2 METHODS AND MATERIALS

DMEPA uses Failure Mode and Effects Analysis¹ (FMEA), lessons learned from postmarketing experiences, and principles of human factors to identify potential sources of errors with container labels, carton and insert labeling. Thereafter, we provide recommendations that aim at reducing the risk of medication errors.

The Applicant submitted container labels and carton labeling on September 29, 2010 as part of a new drug application which includes (b) (4) 0.15 mg: 0.15 mg/0.15 mL epinephrine injection pre-filled auto-injector, (b) (4) 0.3 mg: 0.3 mg/0.3 mL epinephrine injection pre-filled auto-injector, as well as a (b) (4) Trainer device (see Appendices A-C). Additionally, the Applicant submitted a Human Factors Program Report on November 4, 2010 and, on February 1, 2011, the Applicant submitted photos of the Trainer Device Configurations (See Appendices D-F).

3 RECOMMENDATIONS

Our evaluation identified areas of needed improvement in order to minimize the potential for medication errors for this product. We provide recommendations for the package insert in Section 3.1, *Comments to the Division of Pulmonary, Allergy and Rheumatology Products (DPARP)*, and we provide recommendations for the container labels and carton labeling in Section 3.2, *Comments to the Applicant*. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Nichelle Rashid at 301-796-3904.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

3.1 COMMENTS TO THE DIVISION:

1. Revise the following abbreviations throughout the package insert labeling as follows:
 - a. “≥” to read “greater than or equal to”
 - b. “<” to read “less than”
 - c. “>” to read “greater than”

These abbreviations are considered error-prone because they may be mistaken for the opposite of their intent. As part of a national campaign to warn healthcare practitioners and consumers not to use error-prone abbreviations, acronyms, dose designations, or symbols, including trailing zeroes, FDA agreed not to use such error prone designations in their approved product labeling. Please revise accordingly.

2. Delete the (b) (4) throughout the insert labeling as this information is unnecessary and may lead to confusion.
3. In the HIGHLIGHTS OF PRESCRIBING INFORMATION section, revise the drug name presentation (b) (4) to read “(b) (4) (epinephrine injection, USP) injection” in accordance with USP General Chapter <1> INJECTIONS. [Note the deletion of (b) (4). This product is already in solution and requires no dilution prior to administration.]
4. Revise the DOSAGE AND ADMINISTRATION section of the HIGHLIGHTS OF PRESCRIBING INFORMATION and the FULL PRESCRIBING INFORMATION as follows:
 - a. Please add “lbs” after 33 to read 33 lbs (for example 33 lbs to 66 lbs).
 - b. Please add the statement “Each device is a single-use injection.” after the current statement “Inject (b) (4) intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary.”
5. Revise the FULL PRESCRIBING INFORMATION, INSTRUCTIONS for Use, and additional labeling to reflect changes in the voice script that the Applicant agreed to in correspondence dated March 21, 2011. See Appendices G and H for revised voice scripts.
6. Revise the PATIENT COUNSELING INFORMATION section of the FULL PRESCRIBING INFORMATION, the INSTRUCTIONS for Use, and additional labeling to advise the patient or caregiver of the noise the device emits when the injection occurs. Patients or caregivers may be startled and pull the device away from the body before the injection can occur.

3.2 COMMENTS TO THE APPLICANT:

A. General Comments

1. Based on postmarketing experience we recommend that the Trainer not be packaged in the same carton as the active device. Patients may potentially use an inactive device during an actual emergency. Conversely, patients may get

confused while practicing and accidentally inject themselves or someone else with an active device.

2. We note that any statements on the sides of the Outer Case Label and the Device Label will most likely be covered by the patient or caregiver's hand rendering them useless to the patient and thus, should be relocated to an area of the device visually accessible to the patient.
3. Increase the font size of the middle set of digits in the NDC number (e.g., xxxx-XXXX-xx). These digits are used by pharmacists to ensure that the correct product is dispensed.
4. Revise all container labels and carton labeling (including the written instructions on the front panels of the Trainer and active devices) to reflect the changes in voice script that the Applicant agreed to in correspondence dated March 21, 2011. See Appendices G and H for revised voice scripts.
5. The font color used to express both product strengths is white, thus the two active devices, although different in strength, look similar when compared side-by-side. Ensure the product strengths are well differentiated from one another. The expression of strength should be highlighted by using boxing, shading or some other means and if color is used, they should be different.
6. Incorrect product selection errors may occur because both active devices utilize the same overall color scheme (red-blue-green versus blue-red-green) on the labels and labeling. The use of different color schemes will improve the differentiation between the two products and decrease the likelihood of wrong strength selection errors.

B. Outer Case Label (0.15 mg, 0.3 mg, and Trainer)

1. The triangle symbol at the top of the Outer Case Label may not be understood by patients and caregivers to mean that the device should be pulled out of the case. Please revise so that the statement is more explicit so it is clear how the device separates from its case. One example would be to use the word "pull" instead of (b) (4), as in "pull device from this case", or make the triangle appear more as an arrow symbol.

C. Device, Outer Case Label, and Carton Labeling (0.15 mg and 0.3 mg)

1. Increase the prominence of the established name (epinephrine injection, USP) to be in accordance with 21 CFR 201.10 (g)(2), which takes into consideration not just size of the established name but all pertinent factors, including typography, layout, contrast, and other printing features.
2. Delete the duplicate strength that appears above the proprietary name (in a small box) and increase the prominence of the product strength which follows the established name.
3. Revise the current statement "For single-use injection" to read as follows: "For single-use injection. Refill prescription after use".

D. Device Label, Outer Case Label, and Carton Labeling (Trainer)

1. Delete the proprietary name (b)(4) and replace with “Trainer for (b)(4)”. Note that the proprietary name (b)(4) should appear in a smaller font than the word “Trainer” to decrease the likelihood that the trainer is not mistaken for the active device. Furthermore, the proprietary name should not be used as a stand alone statement on the Trainer labels and labeling; it should always appear as “Trainer for (b)(4)” and be accompanied by the statement “Contains no active drug or needle”.
2. Revise the text color and background color utilized for the Trainer. Grey text on black background may be hard to read, for example, the word “Front” on the bottom of the outer case label. Additionally, black text on grey background, such as the statement “Auto-Injector Trainer” on the side panel of the outer case label, appears difficult to read.

E. Carton Labeling (Trainer)

1. Revise the Trainer carton colors to match the colors of the Trainer device. Currently the Trainer carton color scheme is similar to the carton color scheme utilized for (b)(4) 0.15 mg, thus creating potential confusion between the Trainer and the active device.

F. Physician Sample Outer Case Label and Carton labeling

1. On the principal display panel include the statement “Physician Sample - Not for Sale”.

G. Voice Script

1. Change the audible instructions in the active device and Trainer voice scripts (and associated repeated instructions) to those agreed to in the Applicant correspondence dated March 21, 2011. Additionally, revise the corresponding written instructions on the front panels of the Trainer and active devices. See Appendices G and H for revised voice scripts. Revise as follows:

from: “(b)(4) (b)(4)”

to: “*To inject, place black end against outer thigh, then press firmly and hold in place for 5 seconds.*”

2. Change the injection complete instruction on the active device:

from: “(b)(4) (b)(4)”

to: “*Injection complete. Seek emergency medical attention.*”

3. Change the final Trainer instruction:

from: “(b)(4) (b)(4)”

to: “*This Trainer may be reused for training purposes.*”

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

COLLEEN BRENNAN
04/28/2011

TODD D BRIDGES
04/28/2011

CAROL A HOLQUIST
04/28/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
General Hospital Devices Branch

DATE: APR 07 2011

TO: Ying Wang, OPS/ONDQA/DNDQA III, CDER, WO-21, Room 1633

Cc: Swati Patwardhan, OPS/ONDQA, CDER, WO-21, Room 2623;
Prasad Peri, OPS/ONDQA/DNDQA I, CDER, WO-21, Room 2558;
Office of combination products at combination@fda.gov

THRU: Valerie A. Flournoy, Chief, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66 Room 3526

FROM: M. Isabel Tejero, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66 Room G254

SUBJECT: Inter-Center consult requested by OPS/ONDQA/CDER, to evaluate a comparability protocol for a device manufacturing change. This consult is associated with NDA 201739, Epinephrine Auto-Injectors (EAI) 0.3 mg and 0.15 mg. The application was submitted by Intelliject Incorporated. The EAI device's intended use is the emergency treatment of severe Type I allergic reactions.

INSTRUCTIONS: Evaluate the adequacy of the proposed automated vision inspection during some of the device assembling.

Objective

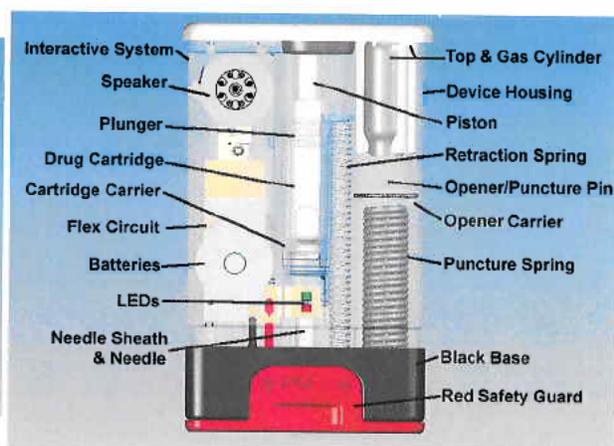
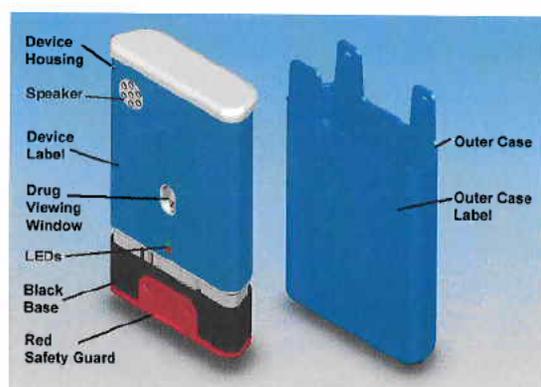
The Office of Compliance at CDRH received a consult request from CDER regarding the Intelliject epinephrine autoinjector (EAI) on March 16, 2011. The consult requested CDRH/OC evaluation of the adequacy of the device manufacturing changes submitted by the firm, Intellijet Inc. The [REDACTED]^{(b) (4)} inspection to automated vision inspection during some of the device assembling.

Product Description

The EAI is an epinephrine prefilled drug-device delivery system. As stated in the Device Master File, the intended use of this combination product is the emergency treatment of severe allergic reactions (anaphylaxis) to stinging insects (eg, order Hymenoptera, which

includes bees, wasps, hornets, yellow jackets and fire ants), and biting insects (eg, triatoma, mosquitos), allergen immunotherapy, foods, drugs, diagnostic testing substances (eg, radiocontrast media), and other allergens, as well as anaphylaxis to unknown substances (idiopathic anaphylaxis) or exercise-induced anaphylaxis. The EAI is intended for immediate administration in patients with a history of anaphylactic reactions.

The manufacturer describes the device constituent of the EAI as a gas powered, needle-based auto-injector that delivers the prescribed dose of epinephrine into the user once activated (see figures bellow for more detail). The needle is fully retracted within the device housing following use. EAI also includes an enhanced labeling feature in the form of an electronic prompt system (also referred to as “interactive system”) that provides audible and visual cues to assist in guiding a user through the injection process. This electronic prompt system works independently from the mechanical functionality of the delivery system in the device.



The manufacturing sites affected by the current proposed manufacturing and site changes are the following:



Consult Evaluation

Upon review of the records provided, CDRH Office of Compliance has established that Intellijet Incorporated, located in Richmond, Virginia, is responsible for the finished epinephrine autoinjectors (EAI) of 0.3 and 0.15 mg dosages respectively. (b) (4)

(b) (4) has been identified as the contract manufacturer in charge of assembling the finished EAI. The firms contact information is the following:

Intellijet Inc.
111 Virginia Street, Suite 405
Richmond, Virginia 23219
FEI: 3007135538 / FEI: 3008406709

(b) (4)

Under the Medical Device Regulations, component manufacturers are not subjected to the QS regulation requirements, under 21 CFR 820.1(a). It follows that manufacturing changes done at these component manufacturers are not regulated. Thus, (b) (4) and ultimately Intellijet, are responsible through their purchasing controls (21 CFR 820.50) to ascertain that any changes made at (b) (4), conform to their product design and quality requirements.

The comparability protocol submitted for comment seems to be adequate to compare the proposed automated processes (b) (4). Intellijet proposes to move some of the needle subassembly processes to (b) (4), automate processes for drug cartridge assembly (b) (4) and automate multiple others at their final assembly and packaging contract manufacturer (b) (4).

Intellijet Inc. has included in this comparability protocol the move of a needle sub-assembly line from (b) (4). This reviewer was not able to find any information about this firm in the submitted protocol or in the paperwork submitted for NDA 201739.

Intellijet proposes the automation of the EAI final assembly line, packaging and inspection, at the (b) (4) facility located at (b) (4). CDRH has several questions about the proposed changes:

1. Does the firm have other processes at the same facility comparable to the new automated assembly the firm is proposing to set up?
2. What manufacturing changes will be conducted to put the new data matrix in the device housing?
3. Does the addition of the data matrix have any impact on the final product safety and effectiveness?

To properly evaluate the manufacturing process of the new assembly lines, CDRH would like to have access to the following information at the time of the review:

1. A diagram of the proposed new manufacturing site.
2. A description of the proposed process flow.
3. A description of the equipment and processes that are the subject of the site change.
4. A list of the processes that will be fully verified, where appropriate, and the verification methods to be used.
5. The process validation or revalidation master plan (including software validation where applicable)
6. The process validation or revalidation information for all processes that were validated. It is recommended that the firms provide the process validation or revalidation protocols, and completed reports for all the processes that required validation. It is recommended that the firm provide all their completed validation activities prior to submitting the comparability study results in case a preapproval inspection is recommended.
7. The procedures for environmental and contamination controls, if such conditions could adversely affect the device.
8. Procedures that explain how inspection, measuring, and test equipment are routinely calibrated, inspected, checked, and maintained. The submission of the complete list of the procedure titles and a sample of the most relevant procedures may be enough for the evaluation. If granted, a statement indicating that procedures are the same as previously submitted should be provided.

CDRH Recommendation

CDRH has evaluated the comparability protocols submitted by Intellijet Inc. to compare the automation changes proposed to increase production of their EAI to commercial standards. The studies proposed and data to be submitted seem adequate to provide a comprehensive comparison between automated and semi-manual inspection within the assembly lines.

However, CDRH considers that the comparability protocol submitted does not address the qualification of the new assembly lines installed at the different locations, and would like more information regarding the installation and validation/verification, as requested above, of the new processes before making a recommendation.

CDRH reserves the final recommendation regarding the proposed changes until the time when the firm submits all records necessary to conduct a thorough evaluation of the adequacy of their proposed site and process changes.



M. Isabel Tejero, MD PhD

Prepared/typed: MITejero: 3/28/2011; 3/31/2011

Reviewed/approved: VAFournoy: *VAF 4/1/11* GKroehling 7 Apr 2011

Finalized:

cc:

WO66-3515 (DOE-A Firm File)

WO66-3515 (Division Chron File)

WO66-G254 (MI Tejero)

CTS No.: CON114543

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/s/

SWATI A PATWARDHAN
04/11/2011
on behalf of CDRH reviewer Dr. Isabel Tejero

MEMORANDUM

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

DATE: April 6, 2011

TO: Badrul A. Chowdhury, M.D.
Director, Division of Pulmonary, Allergy, and
Rheumatology Products (DPARP)
Office of New Drugs

FROM: Abhijit Raha, Ph.D., Pharmacologist
Division of Scientific Investigations (DSI)

THROUGH: Martin K. Yau, Ph.D. _____
Acting Team Leader - Bioequivalence
GLP and Bioequivalence Investigations Branch
Division of Scientific Investigations (DSI)

SUBJECT: Review of EIR Covering NDA 201-739, Epinephrine
Auto-injector, Sponsored by Intelliject, Inc.

At the request of DPARP, DSI audited the following
bioequivalence study:

StudyINT0802: "A Randomized, Single-Blind, Two-Treatment,
Three-Period, Three-Sequence Study of the
Bioavailability of 2 Formulations/Delivery
Devices for Epinephrine in Healthy Human
Volunteers"

The audits of the clinical and analytical portions of study
INT0802 were conducted at Parexel International, Baltimore,
MD and [REDACTED] ^{(b) (4)} respectively.

Clinical Site: Parexel International, Baltimore, MD

Following inspection of the clinical site (March 31 -
April 4, 2011), Form FDA-483 was not issued, and no
significant clinical findings were noted.

Page 2 - NDA 201-739, Epinephrine Auto-injector, 0.15 mg and 0.30 mg

Analytical Site: [REDACTED] (b)(4)

Following inspection at the analytical site (February 14-18, 2011), Form FDA-483 was not issued. No significant findings were noted.

Conclusion:

Following the inspections at the clinical and analytical study sites, DSI recommends that the data from study INT0802 generated at the clinical and analytical sites be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.


Abhijit Raha, Ph.D.

Final Classification:

**Parexel International, Baltimore, MD (Clinical)-NAI
(FEI Number: 3005445577)**

[REDACTED] (b)(4) **(Analytical)-NAI**
(FEI Number: [REDACTED] (b)(4))

cc: DARRTS

CDER DSI PM TRACK
OND/DPARP/Badru1 A. Chowdhury, Angela Ramsey (HFD-570)
HFD-48/Ball/Haidar/Yau/Dejernett/Raha/CF
HFR-CE250/Cynthia A. Harris
HFR-CE8585/Scott B. Laufenberg
Draft: AR 4/06/2011
Edit: MKY 4/06/2011
DSI: 6152; O:\BE\EIRCover\201739.ppd.epi.doc
FACTS [REDACTED] (b)(4)

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/s/

ABHIJIT RAHA
04/06/2011

MARTIN K YAU
04/06/2011



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: March 1, 2011

From: Nikhil Thakur, LCDR USPHS, Combination Product Team Leader WO66, RM 2562
CDRH/ODE/DAGID/General Hospital Devices Branch (GHDB)

To: Angela Ramsey, Senior Regulatory Project Manager WO22 RM3395
CDER/OND/ODEII/DPARP

Subject: CDRH Consult, IND 201739, GEN 1100241, Intelliject, LLC
(Autoinjector to deliver epinephrine)

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding IND 201739. The device constituent of this combination product consists of a custom autoinjection device with a sharps prevention feature to deliver a single dose of epinephrine.

2. Device Description

Intelliject, Inc. (Intelliject) has developed an Epinephrine Auto-Injector 0.15 mg (epinephrine injection USP 1:1000) and an Epinephrine Auto-Injector 0.3 mg (epinephrine injection USP 1:1000), collectively referred to as EAI, or individually referred to as EAI 0.15 mg and EAI 0.3 mg. During development, EAI was previously referred to as (b) (4) and is currently referred to as (b) (4) (brand name under CDER review) in all draft labeling.

The combination product is a prefilled epinephrine drug delivery system. The drug constituent component of EAI comprises 0.76 mL of epinephrine injection, USP 1:1000 (or 1 mg/mL) in a USP Type 1 (b) (4) glass cartridge, of which a single dose of 0.3 mg (0.3 mL) or 0.15 mg (0.15 mL) is delivered by auto-injection into the anterolateral aspect of the thigh, through clothing if necessary. The residual drug cannot be further administered and is discarded with the device. Each EAI is intended for single use only. The device constituent part of the combination product is an auto-injection device.

The device component of EAI is a gas powered, needle-based system that delivers the prescribed dose of epinephrine into the user once activated. The needle is fully and automatically retracted within the device housing following use. The EAI also includes an enhanced labeling feature in the form of an electronic prompt system that provides audible and visual cues to assist in guiding a user through the injection process. This electronic prompt system works independently from the mechanical functionality of the epinephrine delivery system in the device.

A pictorial representation of the device constituent is provided in Figure 1.

Figure 1a. External Components of EAI

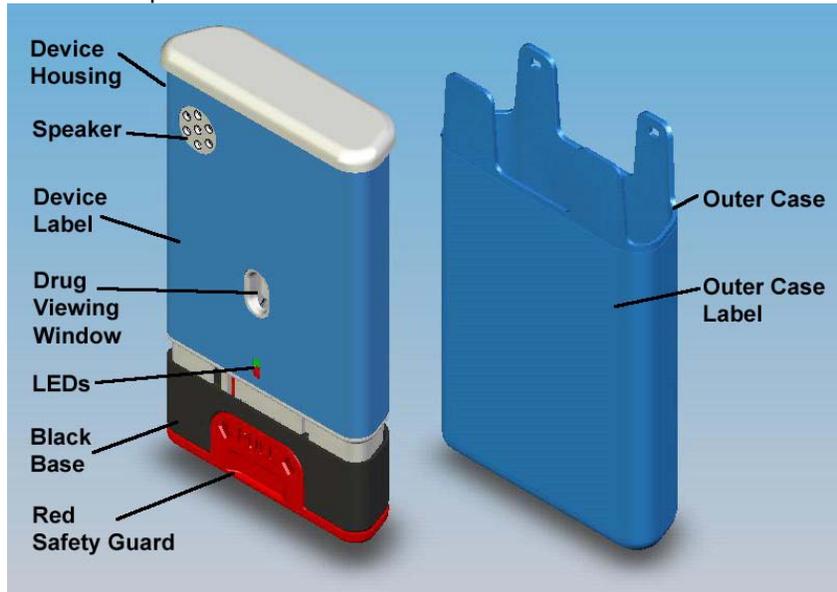
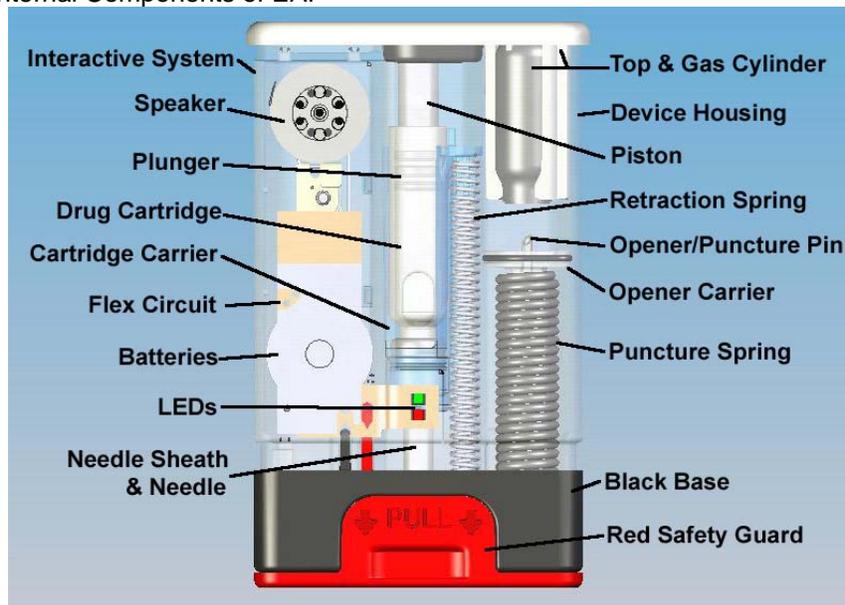


Figure 1b. Internal Components of EAI



The device component of EAI is a self-contained auto-injection device that requires no assembly, priming or attachments. The Outer Case is made of polycarbonate thermoplastic and is designed to protect EAI during normal use and to prevent the epinephrine solution from light exposure. Once the Outer Case is removed, the epinephrine solution can be seen through the drug viewing window. EAI is activated by pulling the Red Safety Guard and pressing the Black Base against the injection site (patient's outer thigh). The Black Base cannot be depressed without removing the Red Safety Guard. This design feature helps prevent premature activation of EAI.

3. Documents Reviewed

IND 201739
MAF (b) (4)

4. CDRH Review and Comments

CDRH's Review of the device constituent for this Combination Product consisted of an assessment of Device Performance, Human Factors, Biocompatibility, Sterilization, Software, and Electrical Safety/Electromagnetic Compatibility (EMC). I had spoken LCDR Alan Stevens, who had reviewed this device in the past as part of Pre-IND 76367 and IND 76367. Unfortunately, I was not able to obtain a copy of the original review memo.

Regarding Device Performance (Bench Testing):

The Sponsor has conducted extensive performance testing to demonstrate that the EAI is functionally safe and effective for its intended use. The list of tests reviewed is provided in Attachment 1 of this memorandum. The Sponsor has successfully demonstrated that their device meets the recommendations stated within the applicable ISO Standards and FDA Guidance documents. Specifically, the Sponsor has demonstrated conformance to:

ISO 11608-1, -2, *Pen Injectors for Medical Use*
FDA Guidance, *Medical Devices with Sharps Injury Prevention Features*, Issued August 9, 2005.
FDA DRAFT Guidance, *Technical Considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products.*, Issued April 2009.

As a result of the functional testing described in Attachment 1, the Sponsor implemented several changes to the device design. These changes were subsequently demonstrated to be safe and effective through performance testing. See Figure 2.

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If you have any questions, please contact Nikhil Thakur at (301) 796 - 5536.

Sincerely,

Nikhil Thakur
Combination Product Team Leader

Concurred By:

Richard Chapman
Branch Chief

ACTING
FOR RICHARD CHAPMAN
BRANCH CHIEF GHD3.
3/1/2011

IND 201739, GEN 1100294
Intelliject, LLC
[Customized Auto Injection Device to deliver epinephrine]

Attachment 1 – Summary of Tests that were reviewed by CDRH.

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IND 201739, GEN 1100294
Intelliject, LLC
[Customized Auto Injection Device to deliver epinephrine]

Attachment 2 –Consult Review from CDRH Human Factors Expert



Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

DATE: February 25, 2011
FROM: QuynhNhu Nguyen, Biomedical Engineer, DAGID/ARDB
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, DAGID
TO: Nikhil Thakur, Combination Products Team Leader, DAGID/GHDB
SUBJECT: NDA 201739 Intelliject Inc.
Human Factors/Usability Review, CON112680

Human Factors Recommendation

The results of the validation studies found in the submission demonstrate that Intelliject has systematically evaluated use related risks, and validated user-performance of the highest priority tasks pertinent to proposed product. I have no further questions.

Review of Applicant's Evaluation of Use-Related Hazards

Material Review

eCopy of the HF Materials in CTS as attachments

Product Description:

Epinephrine Auto-Injector (EAI) is a new, compact, patient-actuated, epinephrine delivery system, that delivers one dose of either 0.3 mL (0.3 mg EAI) or 0.15 mL (0.15 mg EAI) Epinephrine Injection, United States Pharmacopeia (USP) 1:1000 for allergic emergencies (anaphylaxis).

For the Summative Design Validation Study INT0801, EAI that is being presented for FDA approval and market introduction was referred to as (b) (4).” In the INT0801 study, the only difference between the (b) (4) and (b) (4) devices used in the study is that (b) (4) included the electronic system that provides audible instructions and visual cues to assist in guiding the user through the epinephrine delivery steps. In the INT-FE-0901 study, the device was referred to as (b) (4).” A final brand name will be submitted to FDA for approval as a part of the NDA. The device names ‘EAI’, (b) (4), and (b) (4) should be considered interchangeable as this report is reviewed.



Definition of User Population

EAI is intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis. Such anaphylactic reactions may occur within minutes after exposure, and could be fatal. Due to the severity of reactions in both pediatrics and adults and the fact that patients may be incapacitated to self-administer in times of an allergic emergency, the device is

commonly used by caregivers or bystanders (laypersons). Often, users include parents of allergic individuals, babysitters, and restaurant staff. Healthcare professionals also use the device, especially school nurses and emergency medical technicians (EMTs).

Three major HF efforts, the Summative Validation Study (INT0801), Sharps Injury Prevention Feature Validation and Formative Study (INT0803), and Labeling Comprehension and Revalidation Study (INT-FE-0901) included adult subjects, pediatric subjects, parents of food allergic children, as well as subjects with and without prior experience using an auto-injector or familiarity with anaphylaxis, and healthcare professionals, in order to test EAI with a wide-variety of the intended user population.

Intended Use Environment

EAI will be used in the following list of environments. This list is not exhaustive, as there are many other uncommon environments in which the device could be used:

- At Home
- In Restaurants
- In Hospitals
- In Helicopters (Med-Evac.)
- In Emergency Vehicles
- Outdoors
- In Other Vehicles
- In Schools (Nurses Offices)
- In Daycare Facilities
- At Work
- In Airplanes
- Places of Entertainment

Use Scenario

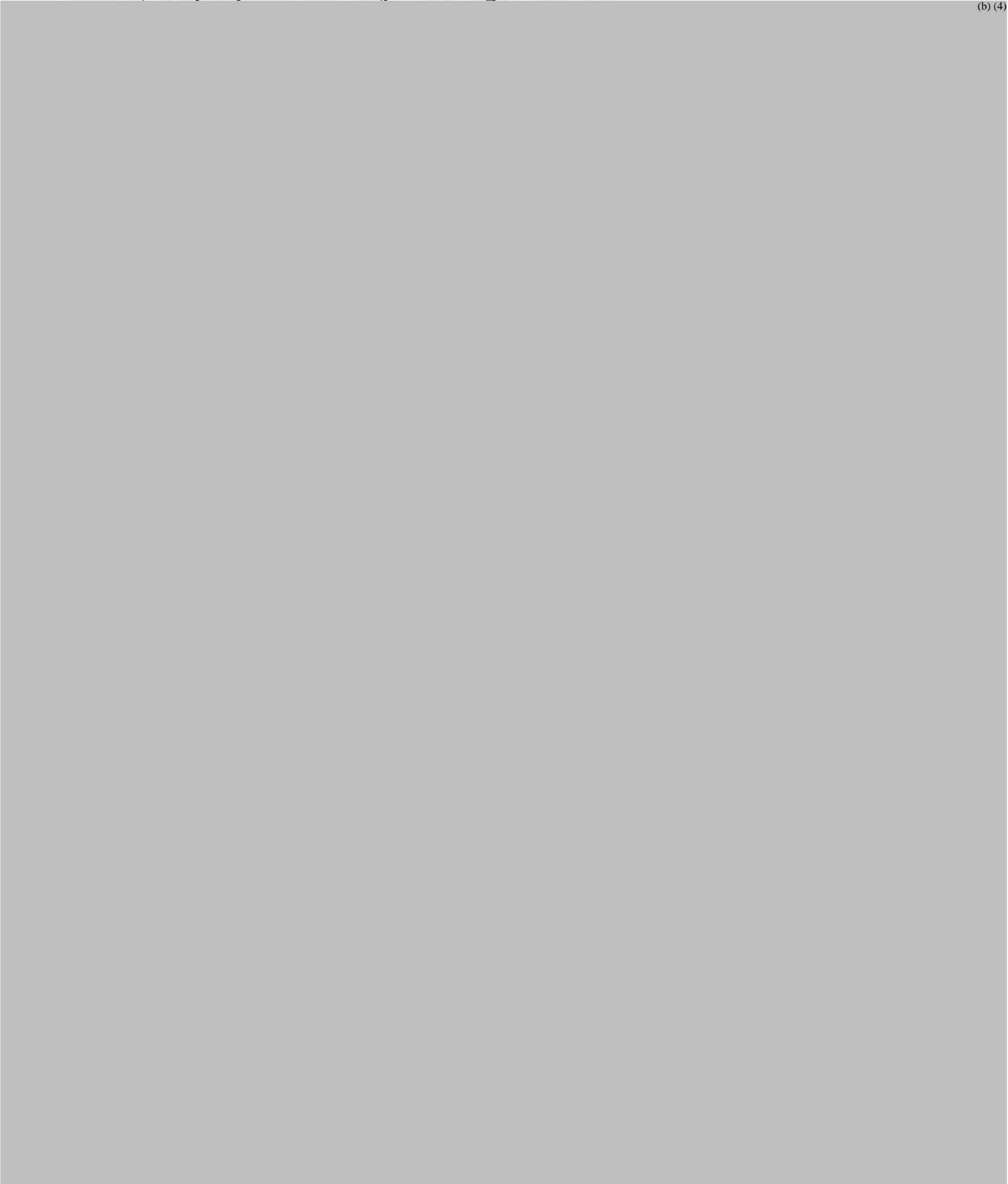
In order to use the device, a user first pulls the outer case down and away from the device housing. At that time, the interactive audible instructions begin. The user then pulls off the red safety guard in order to “arm” the device. Next, the user places the black end of the device against his or her outer thigh (can be injected through clothing) and pushes down firmly on the device housing in order to activate the injection. An audible hiss occurs to provide feedback to the user that the injection is occurring. The user holds the device in place for five seconds, the needle retracts up within the housing, and an audible instruction, as well as a red, blinking LED, provides injection confirmation.

Risk Analysis and Use-Related Hazards

The applicant applied several different analytical and empirical approaches to identify use related hazards associated with EAI including Heuristic Analyses, Hierarchical Task Analysis, and Expert Usability/HF Reviews. A summary of use-hazard risk identification and mitigation was provided in Table 5 of Appendix I.

Summary of Epinephrine Auto-Injector Design Validation

(b) (4)



Subjective user feedback was also collected using a questionnaire. Based on the objective and subjective data, the applicant conducted a post hoc analysis to analyze subject's performance and use errors with the devices in order to determine the residual risk remaining with (b) (4) and (b) (4). The post hoc critical error and residual risk analysis indicated that although adult and pediatric subjects using (b) (4) committed fewer use errors and had an increased probability of receiving a successful injection of epinephrine as compared to the currently marketed epinephrine auto-injectors, **there are still aspects of the product that should be addressed to improve total system performance before market introduction.** These aspects include:

- 1) Redesign the red safety guard with increased tactile features.
- 2) Clarify the red safety guard use instruction in labeling.
- 3) Redesign the voice script for the electronic prompt system to ensure safety guard removal prompt is repeated at appropriate timing.
- 4) Update electronic prompt system to eliminate battery contact intermittency and tear through trace switch malfunctions.
- 5) Revised labeling to more clearly emphasize correct injection location.
- 6) Plan to include text in the Prescribing Information and Patient Information Leaflet that will encourage training of patients prior to use.
- 7) Plan to include a Trainer and Trainer Information Leaflet with each initial prescription.

These changes were subsequently validated in study INT-FE-0901. This study was carried to evaluate a Patient Information Leaflet (PIL) for EAI in a representative sample of 40 participants, and to validate changes in the design of EAI made as a result of the Summative Design Validation Study (Study INT0801). A total of 40 participants were enrolled in this study. The following table shows the percentage of participants who correctly completed the tasks for a successful injection.

Table 18: Percentage of Participants Who Correctly Completed the Tasks Leading to a Simulated Injection

	Pediatric*	Adult*
	n (%)	n (%)
1) Removes Outer Case		
Completed with no issues	19 (95%)	20 (100%)
Completed with issues	1 (5%)	0 (0%)
Did not Complete	0 (0%)	0 (0%)
2) Pulls of Red Safety Guard		
Completed with no issues	19 (95%)	20 (100%)
Completed with issues	1 (5%)	0 (0%)
Did not Complete	0 (0%)	0 (0%)
3) Presses Black End Against the Middle of their Outer Thigh		
Completed with no issues	20 (100%)	20 (100%)
Completed with issues	0 (0%)	0 (0%)
Did not Complete	0 (0%)	0 (0%)
4) Appears to Push Intelliject Firmly Against their Thigh		
Completed with no issues	19 (95%)	17 (85%)
Completed with issues	1 (5%)	3 (15%)
Did not Complete	0 (0%)	0 (0%)
5) Holds Intelliject in Place for 5 Seconds		
Completed with no issues	19 (95%)	20 (100%)
Completed with issues	1 (5%)	0 (0%)
Did not Complete	0 (0%)	0 (0%)
6) Removes Intelliject from the Outer Thigh		
Completed with no issues	20 (100%)	20 (100%)
Completed with issues	0 (0%)	0 (0%)
Did not Complete	0 (0%)	0 (0%)

The study also revealed some non-critical issues that may delay injection; however, each participant was able to eventually complete the task which would have resulted in a successful dose of epinephrine being administered in a timely manner. Only one pediatric participant was unable to complete a step on their first attempt, but was able to complete all steps correctly on the second attempt without issues. Overall, the results indicated that all (100%) participants completed a Successful Injection. Subjective user feedback was collected on the information presented on the Patient Information Leaflet, Label Instructions, and Electronic Voice Prompts System. Nearly all (92.5%) of the participants found the instructions in the PIL to be very easy/simple or easy to follow. Based on the residual risk analysis, there appears to be no additional device design changes are needed that could impact user interaction. The sponsor indicated that several minor labeling recommendations were made with regard to the Patient Information Leaflet and saliency of information. These recommendations will be considered as a part of updates to the labeling submitted to the FDA for final labeling approval.

Human Factors Recommendation

The results of the validation studies found in the submission demonstrate that Intelliject has systematically evaluated use related risks, and validated user-performance of the highest priority tasks pertinent to proposed product. I have no further questions.

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/s/

ANGELA H RAMSEY
03/02/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
General Hospital Devices Branch

DATE: DEC 27 2010

TO: Angela Ramsey, OND/ODEII/DPARP, CDER, WO-22, Room 3395

Cc: Badrul A Chowdhury, OND/ODEII/DPARP, CDER, WO-22, Room 3316;
Office of combination products at combination@fda.gov

THRU: Valerie Flournoy, Chief, General Hospital Devices Branch, Division of
Enforcement A, Office of Compliance, CDRH, WO-66 Room 3526 *VAF-12/27/10*

FROM: M. Isabel Tejero, General Hospital Devices Branch, Division of
Enforcement A, Office of Compliance, CDRH, WO-66 Room G254

SUBJECT: Inter-Center consult requested by DPARP/CDER. This is a pre-market
consult for the 0.3 mg and the 0.15 mg Epinephrine Auto-Injectors (EAI).
The NDA 201739 application was submitted by Intelliject Incorporated.
The EAI device's intended use is the emergency treatment of severe Type
I allergic reactions.

INSTRUCTIONS: Evaluate the need for a pre-approval inspection.

Objective

The Office of Compliance at CDRH received a consult request from CDER regarding the Intelliject epinephrine autoinjector (EAI) on November 8, 2010. The consult requested CDRH's participation in the NDA review process; specifically reviewing the EAI device design and human-factors related studies. CDER also requested the participation of CDRH in the filing/planning meeting scheduled for November 4, 2010 at 10:00 - 11:30am, in WO-22, Room 4201.

The objective of this review by the Office of Compliance is to evaluate the need for a pre-approval inspection based upon the information provided by Intelliject Inc.

Product Description

The EAI is an epinephrine prefilled drug-device delivery system. As stated in the Device Master File, the intended use of this combination product is the emergency treatment of

BEST AVAILABLE COPY

severe allergic reactions (anaphylaxis) to stinging insects (eg, order Hymenoptera, which includes bees, wasps, hornets, yellow jackets and fire ants), and biting insects (eg, triatoma, mosquitos), allergen immunotherapy, foods, drugs, diagnostic testing substances (eg, radiocontrast media), and other allergens, as well as anaphylaxis to unknown substances (idiopathic anaphylaxis) or exercise-induced anaphylaxis. The EAI is intended for immediate administration in patients with a history of anaphylactic reactions.

The manufacturer describes the device constituent of the EAI as a gas powered, needle-based auto-injector that delivers the prescribed dose of epinephrine into the user once activated (see figure 1 bellow for more detail). The needle is fully retracted within the device housing following use. EAI also includes an enhanced labeling feature in the form of an electronic prompt system (also referred to as "interactive system") that provides audible and visual cues to assist in guiding a user through the injection process. This electronic prompt system works independently from the mechanical functionality of the delivery system in the device.

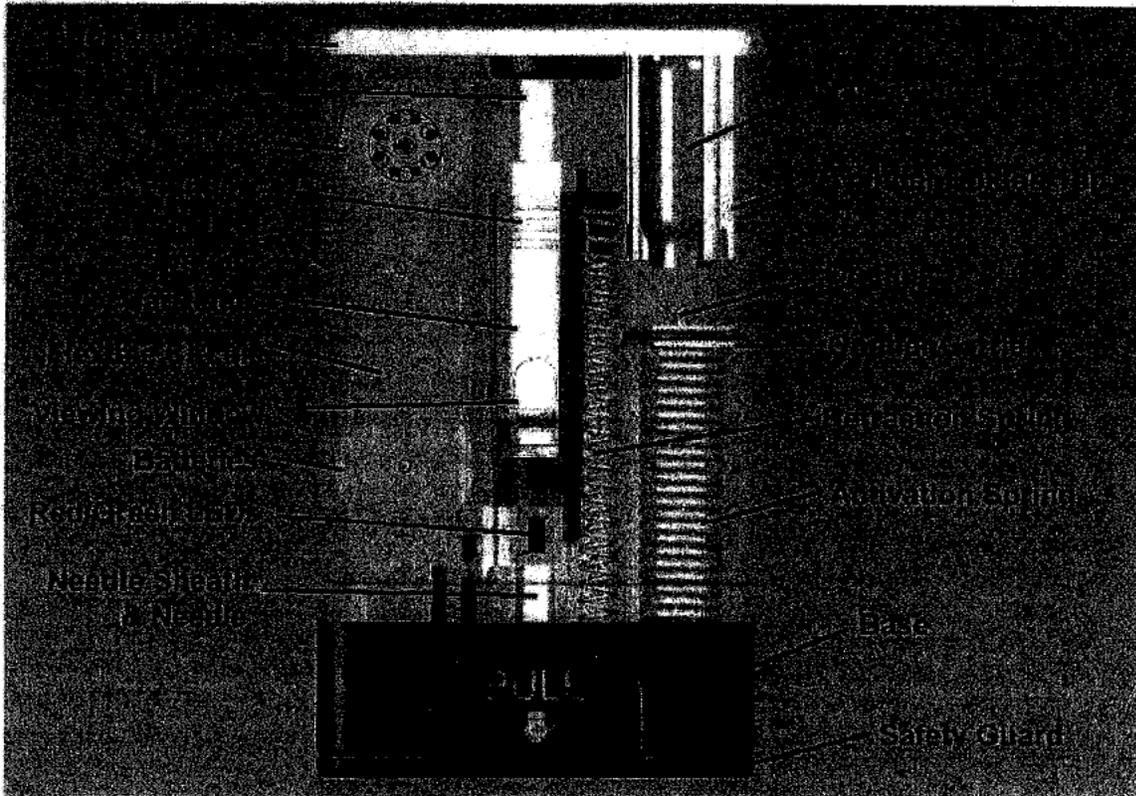


Figure 1: EpiCard™ Primary Components

The manufacturing process of the combination product, EAI, occurs in steps at different facilities:



(b) (4)

Consult Evaluation

Upon review of the records provided, CDRH Office of Compliance has established that Intelliject Incorporated, located in Richmond, Virginia, is responsible for the finished epinephrine autoinjectors (EAI) of 0.3 and 0.15 mg dosages respectively. (b) (4) (b) (4) has been identified as the contract manufacturer in charge of assembling the finished EAI, conducts product performance testing, packaging and labeling.

According to ORA records (FACTS), Intelliject Inc. has not been inspected by FDA. CDRH recommends a Level II QSIT inspection of Intelliject Inc., focusing on Design Controls, Purchasing Controls, Acceptance Activities, MDRs, Complaint Handling, Corrective and Preventive Actions, and Corrections and Removals for the EAI combination product, or a substantially equivalent product. The complete address of this firm is as follows:

Intelliject Inc.
111 Virginia Street, Suite 405
Richmond, Virginia 23219
FEI: 3007135538 / FEI: 3008406709

CDRH also recommends a Level II QSIT inspection of (b) (4) as Intelliject's contract manufacturer responsible for the manufacture of the EAI. This firm has never been inspected by FDA, according to ORA records. CDRH recommends that the investigator focuses on purchasing controls, acceptance activities, and production and process controls. The firm address is as follows:

(b) (4)

CDRH Recommendation

CDRH recommends that the approval of NDA 201739 is deferred until the time when satisfactory pre-approval inspections have been conducted at the sites recommended for inspection above. Attached to this review is an inspection guidance document with inspectional suggestions for the sites CDRH recommends to be inspected.



M. Isabel Tejero, MD PhD

Prepared/typed: MITejero: 12/20/2010

Reviewed/approved: VAFlournoy: *VAF-12/22/10*

Finalized:

GK 12/23/10

cc:

WO66-3515 (DOE-A Firm File)

WO66-3515 (Division Chron File)

WO66-XXX (MI Tejero)

CTS No.: GEN1001394

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/s/

ANGELA H RAMSEY

03/04/2011

Ramsey for Tejero

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: November 15, 2010

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: (Required for international inspections)
Director, Review Division, HFD-570

Director, Division of Pharmaceutical Evaluation, HFD-570

FROM: Angela H Ramsey, Regulatory Project Manager, OND/ODEII/DPARP, HFD-570

SUBJECT: Request for Biopharmaceutical Inspections
NDA 201,739
Epinephrine Auto-injector

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
INT0802	Ronald Goldwater, M.D. Medical Director PAREXEL International LLC 3001 South Hanover St. Baltimore MD 21225 Phone: 410-350-7926 Fax: 410-354-4281 e-mail: ronald.goldwater@parexel.com Gwendolyn P. Painter, M.D., M.P.H., FACOEM, FACPM RTI Health Solutions	<div style="background-color: #cccccc; width: 100%; height: 100%; display: flex; align-items: center; justify-content: center;"> (b) (4) </div>

	200 Park Offices Drive PO Box 12194 Research Triangle Park NC 27709-2194 Phone: (919) 990-8328 Fax: (919) 541-6699 e-mail: wpainter@rti.org RRD International, LLC Kathy Clagett Carr Senior Program Leader RRD International, LLC 7361 Calhoun Place, Suite 325 Rockville, MD 20855-1765 Phone: (301) 762-6100, ext. 124 Fax: (301) 762-6154	

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

_____ Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by May 22, 2011. We intend to issue an action letter on this application by **July 29, 2011**.

Should you require any additional information, please contact Angela H Ramsey, Senior Regulatory Project Manager, at 301-796-2284.

Concurrence: (Optional)

Yun Xu, M.D., Ph.D., Clinical Pharmacology Team Leader (Acting)

Liang Zhao, Ph.D., Clinical Pharmacology Reviewer

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/s/

ANGELA H ROBINSON
11/23/2010