

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208223Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

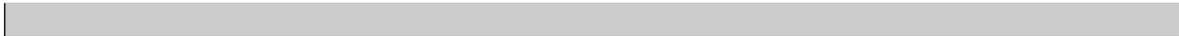
Application Information		
NDA # 208-223	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Zembrace SymTouch Established/Proper Name: sumatriptan Dosage Form: injection Strengths: 3mg/0.5ml		
Applicant: Dr. Reddy's Laboratories		
Date of Receipt: 3/30/15		
PDUFA Goal Date: 1/30/16	Action Goal Date (if different): same	
RPM: Lana Chen		
Proposed Indication(s): migraine with and without aura		

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 by reliance on published literature, or by reliance on a final OTC monograph. *(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 listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 20-080	FDA's previous finding of safety and effectiveness (e.g., clinical or nonclinical or both)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

BE Study demonstrated bioequivalence to Imitrex injection

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 as labeled 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)? *N/A*

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

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 cited reliance on 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 #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Imitrex injection	NDA 20-080	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:

- 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 final OTC drug monograph?

YES NO

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

Name of drug(s) described in a final OTC drug 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 a new dosage strength (3mg/0.5ml)

(Note: The 3 mg strength was previously approved with Imitrex injection, but was not marketed)

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 intended for the same route of administration 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), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

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

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?
N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
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 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)?
N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
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.

No unexpired patents

Listed drug/Patent number(s):

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):
- (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):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (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

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/s/

LANA Y CHEN

01/28/2016

with concurrence from 505b2 committee

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 21, 2016
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 208223
Product Name and Strength: Zembrace SymTouch (sumatriptan) Injection
3mg/0.5 mL
Submission Date: January 19, 2016
Applicant/Sponsor Name: Dr. Reddy's Laboratories
OSE RCM #: 2015-774-2
DMEPA Primary Reviewer: Justine Harris, RPh
DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Neurology Products (DNP) requested that we review the revised prescribing information, container label, carton labeling, and Instructions for Use (IFU) for Zembrace SymTouch (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.^{1 2}

2 CONCLUSION

¹ Harris J. Revised Label and Labeling Review for Zembrace SymTouch (NDA 208223). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 JAN 06. 9 p. OSE RCM No.: 2015-774-1.

² Harris J. Human Factors and Label and Labeling Review for Zembrace (b) (4) (NDA 208223). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 OCT 09. 25 p. OSE RCM No.: 2015-774 and 2015-1489.

The revised prescribing information, container label, carton labeling, and Instructions for Use (IFU) for Zembrace SymTouch is acceptable from a medication error perspective. We have no further recommendations at this time.

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/s/

JUSTINE HARRIS
01/21/2016

DANIELLE M HARRIS
01/21/2016

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

PATIENT LABELING REVIEW

Date: January 13, 2016

To: Billy Dunn, MD
Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

Mathilda Fienkeng, PharmD
Team Leader
Office of Prescription Drug Promotion (OPDP)

From: Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Dhara Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): ZEMBRACE SymTouch (sumatriptan succinate) Injection

Dosage Form and Route: for subcutaneous use

Application Type/Number: NDA 208223

Applicant: Dr. Reddy's Laboratories, Inc.

1 INTRODUCTION

On March 30, 2015, Dr. Reddy's submitted for the Agency's review an Original New Drug Application (NDA) for DNF-11 Injection (sumatriptan succinate). On September 29, 2015 the Applicant submitted a Proprietary Name Review for the Agency to review the proposed proprietary drug name, ZEMBRACE in combination with the proposed device name SymTouch. The proprietary name ZEMBRACE SymTouch was approved by the Agency on November 11, 2015. ZEMBRACE SymTouch (sumatriptan succinate) Injection is indicated in adults for the acute treatment of migraine, with or without aura.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on June 15, 2015, and June 17, 2015, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ZEMBRACE SymTouch (sumatriptan succinate) Injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA Label and Labeling review was completed on January 6, 2016.

2 MATERIAL REVIEWED

- Draft ZEMBRACE SymTouch (sumatriptan succinate) Injection PPI and IFU received on March 30, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on January 6, 2016.
- Draft ZEMBRACE SymTouch (sumatriptan succinate) Injection PPI and IFU received on March 30, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on January 6, 2016.
- Draft ZEMBRACE SymTouch (sumatriptan succinate) Injection Prescribing Information (PI) received on March 30, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on January 6, 2016.
- Draft ZEMBRACE SymTouch (sumatriptan succinate) Injection Prescribing Information (PI) received on March 30, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on November 9, 2016.
- Approved Imitrex (sumatriptan succinate) comparator labeling dated November 19, 2015.

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. In our review of the MG the target reading level is at or below an 8th grade 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 APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU document using the Ariel font, size 10.

In our collaborative 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 is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
01/14/2016

DHARA P SHAH
01/14/2016

MARCIA B WILLIAMS
01/14/2016

MEMORANDUM

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

DATE: January 8, 2016

TO: Billy Dunn, M.D.
Director
Division of Neurology Products (DNP)
Office of Drug Evaluation I (ODEI)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Visiting Associate
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR covering Study DFP-11/CD/002 submitted to
NDA 208223 conducted at Celerion Inc., Tempe, AZ

Inspection Summary:

At the request of the Division of Neurology Products (DNP), the Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of bioavailability study DFP-11/CD/002 at Celerion Inc., Tempe, AZ. At the inspection close-out meeting, no significant deficiencies were observed and no form FDA 483 was issued. The final classification for this inspection is no action indicated (NAI). I recommend that the data for the clinical portion of **Study DFP-11/CD/002** be accepted for further agency review.

Study Number: DFP-11/CD/002 [Celerion Project #: CA15826]

Study Title: "A Randomized Single-Dose, Three-Way Crossover Study to Determine the Relative Bioavailability of DFP-11 Sumatriptan Succinate 3 mg/0.5 mL Injection versus Imitrex® Injection 3 mg/0.25 mL and 6 mg/0.5 mL (both using Imitrex® 6 mg/0.5 mL) Following Subcutaneous Injection in Healthy Adult Male and Female Subjects"

Study Conduct: November 18 - 28, 2014

Clinical Site: Celerion Inc.
2420 West Baseline Road
Tempe, AZ 85283

The inspection of the clinical portion of the study was conducted by investigator Lakecha N. Lewis, at Celerion Inc., Tempe, AZ from December 7 - 17, 2015.

The current audit covered a review of study protocols and amendments, subjects' informed consent forms (ICFs), eligibility documents, screening logs, delegation logs, IP/study drug receipt, storage, accountability, pharmacy drug accountability records, administration/dosing and shipment records, IRB approvals, sponsor/monitoring correspondence, monitoring visit logs, laboratory result reports, hardcopy and electronic source records and electronic case report forms (eCRFs). No discrepancies were observed and there was no under-reporting of AEs. The site retained reserve samples for the study.

No significant issues were observed and no Form FDA 483 was issued at the conclusion of the inspection.

Recommendations:

Following review of the inspectional findings, the clinical data from the audited study at Celerion Inc. were found to be reliable. Therefore, I recommend that the data from Study DFP-11/CD/002 submitted to NDA 208223 be accepted for further agency review.

Yiyue Zhang, Ph.D.
DNDDBE, OSIS

Final Classification:

Clinical

NAI: Celerion Inc., Tempe, AZ

CC:
OTS/OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller/Kadavil
OTS/OSIS/DNDDBE/Bonapace/Dasgupta/Cho/Zhang
OTS/OSIS/DGDBE/Haidar/Skelly/Choi

Page 3 - Review of EIR from Celerion Inc., Tempe, AZ

OND/ODEI/DNP/Dunn/Chen
ORA/PA-FO/LOS-DO/LOS-DIB/Lewis

Draft: ZY 1/6/2016
Edit: CB 01/08/2016
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/Celerion Inc., Tempe, AZ

BE File #: 6960
FACTS: 11562622

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/s/

YIYUE ZHANG
01/08/2016

CHARLES R BONAPACE
01/08/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 6, 2016
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 208223
Product Name and Strength: Zembrace SymTouch (sumatriptan) Injection
3mg/0.5 mL
Submission Date: December 23, 2015
Applicant/Sponsor Name: Dr. Reddy's Laboratories
OSE RCM #: 2015-774-1
DMEPA Primary Reviewer: Justine Harris, RPh
DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Neurology Products (DNP) requested that we review the revised container label, carton labeling and Instructions for Use (IFU) for Zembrace SymTouch (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹ We did not evaluate the Prescribing Information (PI) in this review as negotiations between the Agency and the sponsor are ongoing. We note the proprietary name has changed since our previous review and the corresponding labeling updates include the revision of the name to Zembrace SymTouch.

2 CONCLUSION

¹ Harris J. Human Factors and Label and Labeling Review for Zembrace (b) (4) (NDA 208223). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 OCT 09. 25 p. OSE RCM No.: 2015-774 and 2015-1489

The revised container label and carton labeling is unacceptable from a medication error perspective. The route of administration is printed on labeling without a space between wording making it difficult to read. Additionally, the modifier ‘SymTouch’ does not appear with the name ‘Zembrace’ in the inside of the carton labeling for both the commercial and professional sample labeling. As the modifier is a part of the proprietary name, the modifier should be included with the proprietary name, i.e., Zembrace SymTouch.

3 RECOMMENDATIONS FOR DR. REDDY’S LABORATORIES

We recommend the following be implemented prior to approval of this NDA:

A. AUTOINJECTOR LABEL (COMMERCIAL AND PROFESSIONAL SAMPLE)

1. We note that the route of administration has been relocated to the red space on the label, however, there is no space between the words ‘subcutaneous’ and ‘use’. Please separate the two words so that the route of administration is clear and can be easily read. Additionally, we find that the relocation of the route of administration appears less prominent since it is separated from other important information on the principal display panel. Please consider relocating the route of administration statement under the proper name and dosage form to prevent this information from being overlooked.

B. CARTON LABELING (COMMERCIAL AND PROFESSIONAL SAMPLE)

1. For the commercial carton labeling, see A.1 above.
2. For the professional sample carton labeling, please consider relocating the route of administration statement, ‘for subcutaneous use only’, under the proper name and dosage form to increase prominence.
3. We note that the proposed proprietary name, Zembrace SymTouch, was found to be conditionally acceptable, however, the modifier ‘SymTouch’ does not appear in the inside of the carton labeling for both the commercial and professional sample labeling. As the modifier is a part of the proprietary name, revise the inside of the carton labeling so that the modifier is included with the proprietary name, i.e., Zembrace SymTouch. Please make this change throughout labels and labeling

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

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/s/

JUSTINE HARRIS
01/06/2016

DANIELLE M HARRIS
01/06/2016

M E M O R A N D U M

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

DATE: December 21, 2015

TO: William H. Dunn M.D.
Director (Acting)
Division of Neurology Products
Office of Drug Evaluation I
Office of New Drugs

FROM: Xiaohan Cai, Ph.D. and Hasan A. Irier, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Director (Acting)
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of EIR covering NDA 208223 analytical
inspection conducted at (b) (4)
(b) (4)

At the request of Division of Neurology Products, Office of Drug Evaluation I, Office of New Drugs, Xiaohan Cai, Ph.D. and Hasan Irier, Ph.D. (from the Office of Study Integrity and Surveillance at the Office of Translational Sciences) audited the analytical portion of the following study at (b) (4)
(b) (4)

Application	Study	Drug Product	Sponsor	Recommend
NDA 208223	DFP-11/CD/002 (Celerion Project No. CA15826)	Sumatriptan Succinate 3 mg/0.5 mL Injection	Dr. Reddy's Laboratories Limited	Acceptable

DFP-11/CD/002: "A Randomized Single-Dose, Three-Way Crossover Study to Determine the Relative Bioavailability of DFP-11 Sumatriptan Succinate 3 mg/0.5 mL Injection versus Imitrex® Injection 3 mg/0.25 mL and 6 mg/0.5 mL (both using Imitrex® 6 mg/0.5 mL) Following Subcutaneous Injection in Healthy Adult Male and Female Subjects"

The inspection of the analytical portion of this study was conducted at (b) (4) during (b) (4). The audit included a thorough review of method validation and study records, examination of facility, equipment, electronic laboratory notebooks, and interviews and discussions with the firm's management and staff. Following the inspection of the analytical portion, Form FDA 483 was not issued. OSIS reviewers discussed few items with the firm during the inspection close-out meeting. These items and our evaluation follow:

Discussion Item 1: Full capture of audit trail of Analyst was not enabled for the sumatriptan studies. Specifically, the project audit trail was not available for review.

During the inspection, the system and result table audit trail of Analyst were provided for review for sumatriptan studies. However, the project audit trail of Analyst was not set up correctly thus it was not available for the review. (b) (4) management acknowledged this observation. The firm agreed to correct this error immediately and examine all studies for the audit trail setting.

OSIS Evaluation: Although the Analyst project audit trail was not available to examine entries of Analyst raw data, we did not observe any discrepancy after a careful examination of system audit trail, batch records, and Analyst raw data folder. Therefore, the above observation is unlikely to impact the integrity of the study data.

Discussion Item 2: Inadequate recording of the sample movements during the method validation in the LabNotes. Specifically, the movements of freeze-thaw samples in the first of the six freeze-thaw cycles were inaccurately recorded in the LabNotes.

The time of the sample movement into the freezer during the first of the six freeze-thaw cycles was identified as a late entry without supporting documentation. These samples were used for the freeze-thaw stability evaluation in method validation. (b) (4) acknowledged this observation and agreed that evaluation of the impact of a late entry should be required.

OSIS Evaluation: Although the freeze-thaw sample movement time was not documented accurately for the first cycle, the longest possible exposure of samples on benchtop was within the established length of benchtop stability. The freeze-thaw stability results met the acceptance criteria. Therefore, this observation is unlikely to impact the integrity of data.

Discussion Item 3: Dur

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associates check and c (b) (4). This was not followed.

OSIS Evaluation: We verified that no quality control and (b) (4) were manually integrated and that the limited practice of manual integration did not impact the outcome of the study. The firm stated that currently they do not practice (b) (4) regarding (b) (4) accordingl

Conclusion:

Based on the observations above, OSIS reviewers conclude that the data from the audited study are reliable. Therefore, the reviewers recommend that the analytical portion of the audited study be accepted for further Agency review.

Xiaohan Cai, Ph.D.
OSIS, DGDDBE

Hasan A. Irier, Ph.D.
OSIS, DGDDBE

Page 4 -

Inspected during

(b) (4)

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NAI -

(b) (4)

FEI:

(b) (4)

Hasan Irier -S

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DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Hasan Irier -S,
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Page 5 -
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cc:

OSIS/Kassim/Taylor/Miller/Nkah/Fenty-Stewart/Kadavil

OSIS/DGDBE/Haidar/Skelly/Choi/Cai/Irier

OND/ODE-I/ONP/Dunn

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Labora t nce/INSPECTIONS/BE Program/ANALYTICAL
SITES/ (b) (4) (b) (4) /NDA 208-223_Sumatriptan Succinate

Draft: HAI (b) (4), XC 12/15/15

Edit: YMC 1 5

OSI file# (b) (4)

FACTS: (b) (4)

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/s/

HASAN A IRIER
12/21/2015

XIAOHAN CAI
12/21/2015

YOUNG M CHOI
12/22/2015
sgined on behalf of Sam Haidar

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: November 25, 2015

To: Billy Dunn, M.D., Director, Division of Neurology Products (DNP)
Eric Bastings, M.D., Deputy Director, DNP
Ramesh Raman, M.D., Medical Officer, DNP
Heather Fitter, M.D., Medical Officer, DNP
Lana Y Chen, R.Ph., Regulatory Project Manager, DNP

From: Dhara Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, Team Leader OPDP

Subject: OPDP draft full Prescribing Information (PI) and carton and container labeling comments for Zembrace® (sumatriptan succinate) injection

NDA: 208223

On June 17, 2015, DNP consulted OPDP to review of the proposed package insert (PI), patient package insert (PPI), instructions for use (IFU), and carton and container labeling for the original NDA submission for Zembrace® (sumatriptan succinate) injection (Zembrace).

PI

OPDP reviewed the version of the draft PI obtained from the DNP Sharepoint on November 9, 2015, and our comments are provided below.

PPI and IFU

The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the draft PPI and IFU under a separate cover.

Carton and Container Labeling



(b) (4)



Thank you for your consult. If you have any questions, please contact Dhara Shah (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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

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/s/

DHARA P SHAH
11/25/2015



Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Memorandum of NDA - Initiated in Vivo Bioequivalence Inspection Assignment

Date: November 24, 2015

From: Charles R. Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

To: ORALOSBIMO@fda.hhs.gov

Subject: Premarket Original Surveillance BIMO Inspection Assignment

Preannounce: No

Compliance Program: 7348.001
PAC Code: 48001A
Priority: High
Operation Code: 12 (Domestic Inspection)
31 (Domestic Sample Collection)

Application Number #1: NDA 208223
Product Name: DFP-11 (also known as DFN-11) Sumatriptan Succinate
3mg/0.5 mL Injection
Sponsor: Dr. Reddy's Laboratories, LPP
Survey Nos. 42, 45, 46, & 54
Bachupally, Qutbullapur
Ranga Reddy District 500072
Andhra Pradesh, India
TEL: (091) 800-857-9406



(b) (4)

Protocol Number:

Application Number	Study Protocol Number
NDA 208223	DFP-11/CD/002
	(b) (4)

Inspection Due Date:  (b) (4)

EIR Due Date: (b) (4)

Center Participation: No
Joint Regulatory Agency Participation: No

Establishment(s) for inspection	FEI Number	FACTS Number
Celerion 2420 West Baseline Road Tempe, AZ 85283 TEL: (602) 437-0097 FAX: (602) 437-3386	3009853739	11562622

Note	<p>Please contact the POC Yiyue Zhang by sending an email to yiyue.zhang@fda.hhs.gov prior to the beginning of the inspection or during the inspection to verify the focus and intent of the inspection. We frequently receive real-time information from the review team that may change the focus of the inspection.</p> <p>Please follow the compliance program with emphasis on the specific instructions in the memorandum.</p> <p>If significant deviations are found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data, we request that you expand the scope of your inspection as necessary and contact me immediately.</p> <p>At the end of the inspection, send an e-mail to yiyue.zhang@fda.hhs.gov with any inspection findings and copy of FDA-483 issued. Forward the EIR and exhibits to the contact address mentioned in the inspection memo.</p> <p>Important: forward any post-inspection correspondence from the establishment as soon as possible. All post-inspection correspondence must be reviewed prior to issuing any post-inspection notification of compliance status.</p>
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This inspection memo provides pertinent information to conduct the inspection of the clinical portion of the following bioavailability (BA) studies. This memo is an addendum to the prior inspection memo to include one additional study. Background material is available in ECMS under the ORA folder.

Do not reveal the studies to be inspected, drug names, or the study investigators to the site prior to the start of the inspection. The site will receive this information during the inspection opening meeting. The inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the OSIS POC.

Clinical Site: Celerion
2420 West Baseline Road
Tempe, AZ 85283
Tel: (602) 437-0097
Fax: (602) 437-3386

NDA 208223

Study Number #1: DFP-11/CD/002 [Celerion Project #: CA15826]

Study Title: "A Randomized Single-Dose, Three-Way Crossover Study to Determine the Relative Bioavailability of DFP-11 Sumatriptan Succinate 3 mg/0.5 mL Injection versus Imitrex® Injection 3 mg/0.25 mL and 6 mg/0.5 mL (both using Imitrex® 6 mg/0.5 mL) Following Subcutaneous Injection in Healthy Adult Male and Female Subjects."

Investigator: Terry E. O'Reilly, MD

of Subjects: 36

(b) (4)

(b) (4) Celerion, Tempe, AZ

(b) (4)

(b) (4)

Table 1

(b) (4)

SECTION A - RESERVE SAMPLES

Because Study DFP-11/CD/002 (b) (4) are bioavailability studies and (b) (4) e studies, there is no regulatory requirement for retention of reserve samples. However, CDER review division has requested collection of reserve samples for Study DFP-11/CD/002.

During the clinical site inspection, please:

- Verify that the site retained reserve samples. Because there is no regulatory requirement, Form FDA 483 should not be issued if the (b) (4) n reserve samples for study DFP-11/CD/002 (b) (4)
- If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve

samples are representative of those used in the specific studies, and that samples were stored under conditions specified in accompanying records.

- Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

SECTION B - CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Data Audit Checklist:

- Confirm that informed consent was obtained by _____ 002 _____ (b) (4) cts
- Audit the study _____ 0 _____ (b) (4) dy
- Compare the study report submitted to FDA with the original documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
- o Number of subject records reviewed during the inspection: _____
 - o Number of subjects screened at the site: _____
 - o Number of subjects enrolled at the site: _____
 - o Number of subjects completing the study: _____

- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- Confirm that adequate corrective actions were implemented for observations cited during the last inspection (if applicable).
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the OSIS POC prior to the inspection. Therefore, we request that the OSIS POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to the OSIS POC (see below). If it appears that the observations may warrant an OAI classification, notify the OSIS POC as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the OSIS POC.

OSIS POC: Yiyue Zhang, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

Tel: (240) 402-6559
Fax: (301) 847-8748
E-mail: yyiyue.zhang@fda.hhs.gov

The endorsed EIR and Form 483 documents should be sent to the following:

If electronic: CDER-OSIS-BEQ@fda.hhs.gov

If paper: Ms. Dinah Miller
FDA/CDER/OTS/OSIS
WO51 RM5333 HFD-45
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Email cc:
ORA/PA-FO/LOS-DO/LOS-DIB/Maxwell
OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Kadavil/Miller
OSIS/DNDBE/Bonapace/Dasgupta/Cho/Zhang
OSIS/DGDBE/Haidar/Skelly/Choi

Draft: YZ 11/19/2015
Edit: CB 11/24/2015
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/Celerion, Tempe, AZ

BE File#: 6960
FACTS: 11562622

BE File#: 7017
FACTS: 11562622

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/s/

YIYUE ZHANG
11/24/2015

CHARLES R BONAPACE
11/24/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Doc Mail Center – WO66-0609
Silver Spring, MD 20993-0002

InterCenter Consult Memorandum
ICC 1500166/NDA 208223

Date: 11/20/2015

To: Dahlia A. Woody, M.S., PMP, FAC-P/PM
Regulatory Business Process Manager
Office of Program and Regulatory Operations
OPQ/CDER

From: Sapana Patel, PharmD.
Pharmacist
WO66 Rm 2562
CDRH/ODE/DAGRID/GHDB

Subject: CDRH Consult for NDA208223/ICC1500166
DFN-11(sumatriptan injection)

Recommendation:
CDRH recommends NDA approval of the device constituent part of the sumatriptan autoinjector.

I. Consult Purpose

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 208223. The device constituent of this combination product consists of a prefilled syringe, ready to use, single dose disposable autoinjector designed to deliver sumatriptan at a concentration of 3mg/0.5ml for subcutaneous injection.

II. Review Summary

The CDRH reviewer performed a review of the prefilled autoinjector, device constituent part for the drug sumatriptan in the concentration of 3mg/0.5ml. This drug is to be administered subcutaneously and is indicated for the acute treatment of migraine with or without aura in adults (b) (4). The sponsor states the injection will be marketed as a prefilled syringe, ready to use, single dose fully assembled disposable autoinjector. The autoinjector consist of a single use injector with the prefilled syringe driven by a plunger in a preloaded state.

Consultants for this file:

Jason To/Sarah Mollo Ph.D-Engineering review of autoinjector
Bifeng Qian Ph.D-Biocompatibility review of autoinjector

The review of this application covered the following:

Auto-Injector:

The review of this application did not cover the following:

Review of the prefilled syringe (primary container closure) including biocompatibility and sterility

Review of the drug product

Manufacturing of the drug product

Review of the safety and efficacy of the drug product after contacting the device constituent parts or while stored in the device constituent parts,

Review of the final drug kit packaging

Device Constituent part usability or human factors validation information

Stability of the drug product after aging

III. Documents reviewed

Documents reviewed related to the design of the device constituent parts for the combination product. This review is limited to the design requirements and verification/validation information to support the device constituent. This review does not cover the review of the primary container closure system (prefilled syringe (PFS)), manufacturing or process validation of the device, nor usability.

NDA 208223

(b) (4)

IV. Review

Indications for Use:

DFN-11 is composed of sumatriptan, a serotonin (5-HT_{1B/1D}) receptor agonist (triptan), indicated for acute treatment of migraine with or without aura in adults (b) (4).

Dosage and Administration:

The maximum single recommended adult dose of DFN-11[®] for the acute treatment of migraine (b) (4), (b) (4), (b) (4) is 3 mg injected subcutaneously. (b) (4),

Administration using DFN-11:

DFN-11[®] is available as a prefilled, ready-to-use, single dose, disposable auto-injector ((b) (4)) containing 3 mg sumatriptan. With this device, the needle penetrates approximately 6 mm. The injection is intended to be given subcutaneously, and intramuscular or intravascular delivery must be avoided. Instruct patients on the proper use of DFN-11[®] and direct them to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle.

Device Description:

The sumatriptan 3mg/0.5ml injection (DFN-11) consists of a prefilled, ready to use, single dose disposable auto-injector ((b) (4)). The pen injector comprises of the final finished delivery system which contains the primary container closure system.

A. Container Closure System:

Information on the container closure system was found in Section 3.2.P.7. This part of the review serves as

identifying the components and specifications of the primary closure.

Primary Container/Closure Components

Container	Packaging Designation	Description	Supplier
Syringe barrel (b) (4)	Primary		(b) (4)
plunger	Primary		

The primary container closure system comprises of the prefilled syringe (syringe barrel and (b) (4) plunger). The syringe barrel is manufactured and supplied by (b) (4) as (b) (4) TM for (b) (4) syringe. The selection of syringe barrel was based on tight tolerance specifications to support an autoinjector design and function, and its suitability for proposed product. DFN-11 Injection uses a (b) (4) syringe, manufactured and supplied by (b) (4) as (b) (4) TM for (b) (4) syringe (Product Identification

(b) (4)). The syringe is a single use, sterile ready to fill (b) (4) TM component with staked needle and 1ml capacity barrel. The needle is 29 gauge 0.5inch and (b) (4) (b) (4). The needle is thin walled, covered with Rigid Needle Shield (RNS) and made of (b) (4).

The syringe barrel is provided as a sterile (b) (4) ready to fill configuration. The syringe is received and accepted by (b) (4) based on its incoming raw material specification and vendor's certificate of conformity (b) (4), which provides assurance that the syringe component meets the requirements for the tests/parameters.

Test	Specification
Visual Identification	Clear (b) (4) barrel with fixed needle and needle shield
Certificate of Conformity Review	Correct material, vendor & grade; meets manufacturer's Specifications
Drawing review	Corresponds to drawing no. (b) (4) rev. 2 on page four
Length	(b) (4)

The following DMFs are referenced for the syringe barrel. They were not reviewed as part of the device review: (b) (4)

The plunger, part of the sterile barrier of the primary closure system consists of a (b) (4) (b) (4) plunger closure ((b) (4)) supplied by (b) (4) Services. The (b) (4) are (b) (4) and ready to use. The sterile (b) (4) plunger is accepted by (b) (4) based on its incoming raw material specification (Attachment 3.2.P.7-1) and vendor's certificate of analysis (Attachment 3.2.P.7-2; (b) (4)), which provides assurance that the (b) (4) plunger meets the acceptance criteria for the tests/parameters listed in Table 3.2.P.7-4 and Table 3.2.P.7-5, respectively.

Test	Specification
Visual Identification	(b) (4) plunger (b) (4)

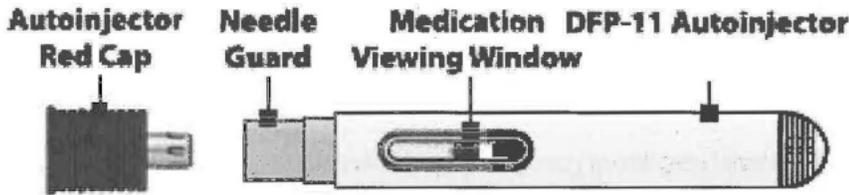
Certificate of Analysis Review	Correct material, vendor and grade; meets manufacturer's Specifications
Certificate of Analysis Review	Corresponds to drawing no. (b) (4)
Length	(b) (4)
Outer Diameter	(b) (4)

(b) (4) (b) (4)

Reviewer Note:
 This part of the review serves as identifying the components and specifications of the primary container closure system. The review of the primary container closure system (syringe barrel and (b) (4) plunger) in its entirety is deferred to CDER.

B. DFN-11 Auto Injector

The autoinjector which is referred to within the submission also as DFN-11 and/or DFP-11 is a fixed single dose, disposable spring powered device based on (b) (4) designed and developed by (b) (4).



The finished autoinjector consists (b) (4)
 (b) (4)
 1.0ml pre-filled USP Type I glass syringe with 29 gauge thin wall and 1/2 inch long staked needle and Rigid Needle Shield (RNS).

(b) (4)

Pre-filled Syringe (PFS)

(b) (4) 1.0 mL pre-filled USP Type I glass syringe with 29 gauge thin wall and 1/2 inch long staked needle and Rigid Needle Shield (RNS), containing 0.5mL sterile solution of sumatriptan succinate.

(b) (4)

(b) (4)

(b) (4)

Method of Use and Operation of the Autoinjector (Section 3.2.P.7.4.4)

The device is provided to the user as a ready-to-use single dose autoinjector designed to deliver the entire labelled contents of the prefilled syringe with one injection stroke. The injection cycle does not require priming and has no capability for delivering a partial dose.

Step 1 - Remove the Cap: Pull the red cap from the device which also removes the RNS. The needle is exposed, but shielded by the yellow needle cover (pictured below).

Step 2 - Place the device on the injection site: The user places the device vertically on the injection site.

Step 3 – Perform Injection: Press the device into the injection site. The retraction of the needle cover activates the device and the injection begins. When the injection begins, the user can hear an audible click. The user will hear a second audible click (upon hearing the second click, the user will continue to hold the injector down and slowly count to 5), which is an indication that the device is nearing the end of the injection process. At the end of injection, the red Plunger Rod will be visible through the Body window. The injection is complete.

Step 4 - Remove device from injection site & dispose of device: The user lifts the device straight away from the skin. The Needle Cover (also known as Needle Guard) will extend outward and lock into place, reducing the potential of needle stick injuries. The user confirms that the red plunger rod has filled the viewing window to ensure full dose delivery. The used device is then capped and disposed in a sharps container or other approved puncture-resistant container.

Device Constituent Part- Design Review:

This section of the review was completed by Jason To and Sarah Mollo Ph.D.

The section below details the consultant's review of information submitted to NDA 208223 and associated master file submissions for the injector devices. This master file is referenced as (b) (4).

A. Essential Performance of the Combination Product

The sponsor identified a list of Key Product Attributes that are essential performance requirements for their autoinjector/combination product:

There are several functional tests, attribute tests, functional/performance requirements under normal conditions, storage & robustness requirements, free fall test and visual testing requirements, which have been derived from the design input requirements for DFN-11 (b) (4). Of all the attributes which have been evaluated as part of design verification testing, four key attributes are included as part of the DFN-11 combination drug/device product: Activation Force, Needle Extension (Injection Depth), Injection Time, and Deliverable Volume. These four attributes are part of the release and stability specifications for DFN-11 and shown in the DFN-11 product specifications in Section 3.2.P.5.1, as well as shown with the stability data presented in Section 3.2.P.8.3.

- *The activation force establishes the amount of force required to activate the device in order to produce an injection. The specification during development was kept at 'Report Results' and will be tightened for process validation and commercial manufacturing once sufficient experience with the commercial tool set becomes available.*
- *The needle extension attribute also referred to as injection depth determines the length of needle that will be under the skin during an injection and represents the depth of an injection. This attribute is established as 6.0 (b) (4) mm.*
- *Injection time represents the amount of time required to complete an injection, to deliver the desired volume. This attribute is established to be (b) (4).*
- *Deliverable volume represents the amount of drug product volume delivered during an injection and has been established based on the density of drug being (b) (4). The deliverable volume specification has been established to be (b) (4).*

B. Design Verification/Performance Testing

Section 3.2.P.7 of the submission contains a summary of attributes tested during Design Verification for the DFN-11 autoinjector device as well as a statement confirming that all testing was performed per ISO standard tests. The parameters tested are derived from the design input requirements for DFN-11 (b) (4) and include functional tests, attribute tests, functional/performance requirements under normal conditions, storage & robustness requirements, free fall test and visual testing requirements. The results from the design verification testing are provided in Table 3.2.P.7-12.

(b) (4)

HUMAN FACTORS AND LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review: October 9, 2015

Requesting Office or Division: Division of Neurology Products (DNP)

Application Type and Number: NDA 208223

Product Name and Strength: Zembrace (b) (4) (sumatriptan) Injection
3mg/0.5 mL

Product Type: Drug-Device Combination Product

Rx or OTC: Rx

Applicant/Sponsor Name: Dr. Reddy's Laboratories

Submission Date: April 2, 2015

OSE RCM #: 2015-774 and 2015-1489

DMEPA Primary Reviewer: Justine Harris, RPh

DMEPA Team Leader: Danielle Harris, PharmD, BCPS

DMEPA Associate Director: Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

Dr. Reddy's Laboratories submitted this NDA to introduce Zembrace (b) (4) (sumatriptan) Injection, 3 mg/0.5 mL, single-dose, pre-filled, disposable autoinjector indicated for the treatment of migraine (b) (4) (b) (4) in adults. Thus, the Division of Neurology Products (DNP) requested that DMEPA review the human factors (HF) validation study results and proposed labels and labeling to determine whether the product can be used safely and effectively as intended.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 HUMAN FACTORS STUDY

Zembrace (b) (4) is provided in a 3 mg/0.5 mL, single-dose, pre-filled, disposable autoinjector indicated for the treatment of migraine (b) (4) (b) (4) in adults. The autoinjector automatically delivers the entire contents of the prefilled syringe (b) (4). Visual indicators viewable in the inspection window (red indicator/plunger rod movement) and audible indicators (2 clicks) inform the user of proper use including the start and end of injection.

The HF validation study evaluated migraine patients (intended users of this product) divided into 3 sub-groups of 15 participants each: trained naive¹, untrained naive, and untrained

experienced² participants. All participants were assessed on their performance of one unaided injection, into either the thigh or upper arm, and their IFU reading comprehension. Additionally, participants were asked to provide feedback on the IFU and packaging. Objective and subjective data were collected for each of the three groups.

All participants were successful in administering a full dose injection, unaided, without patterns of failures or use errors. Additionally, all participants were successful in opening the packaging and removing the autoinjector, identifying the allowable injection sites, checking the expiration date, cleaning the injection site, waiting 5 seconds following the second click, and properly disposing of the device after use. The majority of participants (95%) referred to the IFU while performing the injection and the two participants who did not refer to the IFU successfully administered their unaided injection without difficulties.

Although all participants were successful in administering an unaided injection during testing, we note that four participants commented that they had trouble confirming if the injection was complete as they were not able to see the red in the medication-viewing window from their injection angle or the window looked different from the figure in the IFU. The figure for Step 4A *Confirm Red Color in Medication Viewing Window* shows a red plunger rod (b) (4) (b) (4) (b) (4) stopper, which is visible in the window. This was confusing for the participants. The sponsor addressed this after the study by changing the figure in Step 4a of the IFU to more clearly show the plunger rod and (b) (4) stopper in the window. We agree with the proposed change to the IFU graphic and will not require validation of this change to the IFU.

During the subjective assessment, a few participants indicated they did not hear the first click or misinterpreted the second click to be the first click even though they completed the injection correctly. We note that there is a dedicated statement and image in the IFU that clearly shows that the device produces a start and end click to communicate when the injection started and is complete. Additionally, there is a window indicator to provide a visual feedback mechanism as well. We considered whether a louder audible click might further minimize the risk for use errors; however, increasing the volume on the click may have the unintended consequence of startling patients, resulting in pulling away before the injection is complete. Without substantial changes to the design of the product that is validated by further testing, it is unclear whether this change would be successful in further mitigating the risk for use errors without introducing a new hazard. Thus, we do not recommend any changes at this time to either the product design or other aspects of the user interface such as the IFU.

The sponsor intends to make minor revisions to further enhance the IFU based on user feedback. None of the intended revisions are substantive or involve major changes in the IFU to critical tasks, nor are the changes likely to introduce new risks. Therefore, we agree they can

¹ “Naïve” patients defined as migraine patients who currently only use oral medications to treat their migraine symptoms and have no injection experience.

² “Experienced” patients defined as migraine patients who were injection experienced users of the Sumatriptan StatDose injection device or other injectable migraine medications.

be implemented without requiring another HF validation study. A summary of the methods and results from the summative study for the trained and untrained participants is presented in Appendix C.

3.2 LABELS AND LABELING

Our review of the Prescribing Information (PI) identified areas of vulnerability that can be improved from a medication error perspective as follows:

-  (b) (4)
- In Section 2.2 *Administration Using Zembrace*, the sentence “The injection is intended to be given subcutaneously,  (b) (4)
- In Section 16, *How Supplied Storage and Handling*, the strength statement (3 mg/0.5 mL) is missing. Furthermore, the storage temperatures lack corresponding “C” or “F” after each numerical value and should be revised to add clarity and ensure proper storage of the product.

We note that the salt ‘succinate’ is not present on the carton and container labels nor the dosage strength and volume (3 mg/0.5 mL). We consulted the Office of Pharmaceutical Quality (OPQ) for guidance on the labeling of the product. OPQ confirmed that labeling should state that the product contains sumatriptan succinate; however, since the labeled potency is based on amount of sumatriptan base, the established name should be “sumatriptan injection.” OPQ confirmed the labels should also state the total strength of the injectable volume (i.e. 3 mg/0.5 mL). OPQ will address these deficiencies in their review.

In addition, we note that the route of administration is not displayed prominently on the carton labeling and container labels. We provide recommendations in Sections 4.1 and 4.2 below to address this identified concern.

4 CONCLUSION & RECOMMENDATIONS

The Human Factors validation study demonstrated that intended migraine patient users are able to use the proposed product safely and effectively. We find the results of the HF validation study acceptable and have no further recommendations related to Human Factors testing.

Our review of the proposed labels and labeling identified areas that can be improved to increase the readability and prominence of important information to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information

(b) (4)

B. Full Prescribing Information

1. In Section 2.2: To prevent misinterpretation of the correct route of administration, we recommend revising the statement “(b) (4) (b) (4) to read, “The injection is intended to be given subcutaneously. Do not administer by any other route.”
2. In Section 16, *How Supplied Storage and Handling*, we recommend including the strength statement (i.e. 3 mg/0.5 mL).
3. Section 16, *How Supplied Storage and Handling*, and in the *Patient Information* we recommend revising all storage temperatures to have a corresponding “C” or “F” after each numerical value (i.e., 20° and 25°C (68° and 77°F) and 15° and 30°C (59 and 86°F). Revise throughout labels and labeling where applicable for consistency.
4. See A. 2 above.

4.2 RECOMMENDATIONS FOR THE DR. REDDY’S LABORATORIES

We recommend the following be implemented prior to approval of this NDA 208223:

A. Autoinjector Label (COMMERCIAL AND PROFESSIONAL SAMPLE)

1. To avoid the route of administration from being overlooked, present the statement “For subcutaneous use only” as a separate line and use a larger font, bolding or other means to increase prominence.
2. Separate the manufacturer information from other important information on the principal display panel as it takes readers attention away from important information such as route of administration and storage information.
3. For clarity, revise all storage temperatures to have a corresponding “C” or “F” after each numerical value (i.e., “20° and 25°C” should be revised to read “20°C and 25°C”).
4. Consider removing or relocating the graphic design that is next to the proprietary name. As presented, it competes for prominence with the proprietary name and could be mistaken as the letter “O” and part of the proprietary name.
5. We note that the proposed proprietary name, Zembrace (b) (4) was found to be conditionally acceptable, however, the modifier (b) (4) appears separate from the root name ‘Zembrace’. As the modifier is a part of the proprietary name, revise the labels so that the modifier is included with the proprietary name, i.e., Zembrace (b) (4). Please make this change throughout labels and labeling.

B. CARTON LABELING (COMMERCIAL AND PROFESSIONAL SAMPLE)

1. See A. 1, A.3, A.4, A.5 above
2. We note that in the inside of the carton labeling there are placeholders for a toll free number and a website that patients may access for information about the product. Please provide this phone number and website on the labeling.

C. INSTRUCTIONS FOR USE

1. See A.5 above

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table two presents relevant product information for Zembrace (b) (4) that Dr. Reddy’s Laboratories submitted on April 2, 2015, and the reference listed drug (RLD).

Table 2. Relevant Product Information for Zembrace (b) (4) and the Reference Listed Drug		
Product Name	Zembrace (b) (4)	Imitrex Stat Dose (NDA 020080)
Initial Approval Date	N/A	December 28, 1992
Active Ingredient	Sumatriptan base, as succinate	Sumatriptan Succinate
Indication	1) the acute treatment of migraine attacks with or without aura (b) (4) (b) (4)	1) the acute treatment of migraine attacks with or without aura and 2) the acute treatment of cluster headache episodes.
Route of Administration	subcutaneous	subcutaneous
Dosage Form	single-dose prefilled syringe integrated into an autoinjector pen	prefilled single dose prefilled syringe cartridges for use with the Imitrex Statdose Pen
Strength	3 mg/0.5 mL	4 mg and 6 mg
Dose and Frequency	3 mg at onset of migraine; may repeat if needed \geq 1 hour after initial dose. Maximum: (b) (4)	Acute treatment of migraine: 1 mg to 6 mg Single dose. <ul style="list-style-type: none"> • Acute treatment of cluster headache: 6-mg Single dose. • Maximum dose in a 24-hour period: 12 mg, Separate doses by at least 1 hour.
How Supplied	Prefilled, single-use, disposable injection device; box of 4 autoinjectors.	IMITREX STATdose System [®] , 4 mg, containing 1 IMITREX STATdose Pen, 2 prefilled single-dose syringe cartridges, and 1 carrying case. IMITREX STATdose System, 6 mg, containing 1 IMITREX STATdose Pen, 2 prefilled single-dose syringe cartridges, and 1 carrying case Refill cartridges: Two 4-mg single-dose prefilled syringe cartridges for use with IMITREX STATdose System; Two 6-mg single-dose prefilled syringe cartridges for use with IMITREX STATdose System
Storage	Controlled room temperature of 15°C - 30° C (59°F - 86°F)	Store between 2° and 30°C (36° and 86°F). Protect from light

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 2, 2015, we searched the L: drive using the terms, Zembrace (b) (4) to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews.³⁴

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

Study Objectives:

1. Validate that the Dr. Reddy's DFP-11 autoinjector including the device labeling, and associated Instructions for Use (IFU), can be correctly, safely, and effectively used by the intended user audiences (migraine patients) without patterns of (preventable) use errors that would result in harm to a patient or user.
2. Validate the device design, labeling, and IFU as successful in mitigating high risks and use contexts.
3. Validate that there are no residual risks associated with the device design, labeling or instructions that lead to confusion, high-risk errors, or patient safety risks.

Study Participants:

A total of forty-five participants were included in the study. All participants were patients who regularly experience migraines and were either on oral or injectable medication(s) to treat their migraines. Included in the study were a mix of injection experienced and injection naive participants.

1. **Injection Naive Trained Users (N = 15):** This group represented a user with no injection experience and who would transition from oral medication to their first injection device. All participants were trained.
2. **Injection Naive Untrained Users (N = 15):** This group included a second set of injection naive users on oral medications, with no injection experience, who were instructed to self-educate on the device and injection procedure (worst case scenario).
3. **Injection Experienced Untrained Users (N = 15):** This group consisted of adult migraine patients who were injection experienced uses of the Sumatriptan StatDose injection device or other injectable migraine medications. This group represented users who would be switched from their current medication to the Dr.Reddy's autoinjector. Participants were instructed to self-educate on the device and procedure.

³ Harris, J. Proprietary Name Review for Zembrace (b) (4), IND 118668 and NDA 208223, Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); Insert Date As 2015 JUL 1. RCM No.: 2015-49677 and 2015-81151.

⁴ Neupauer, D. DFP-11 (Sumatriptan Succinate) Injection Human Factors Protocol Review IND 118668, Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); Insert Date As 2014 SEP 16. RCM No.: 2014-1565.

	User Group 1	User Group 2	User Group 3
Injection Experience	Injection Naïve	Injection Naïve	Injection Experienced
Training Condition	Trained	Untrained	Untrained
	N=15	N=15	N=15

Training: One-third of the participants (15/45, 33%) were trained by the moderator. Participants received a brief (approximately 10 minutes) representative training from the moderator. Training consisted of a verbal walkthrough of the full procedure, including autoinjector components, storage, preparation, and administration of the medication. Participants were given time to review the IFU on their own and asked to demonstrate the administration procedure (without actually injecting) for the moderator. If deemed eligible to participate in the study, they were reminded to come for their second session time, which was 2 to 3 days later.

C.2 Tasks Studied and Results

8.1a Summary of Results – All Performance Measures

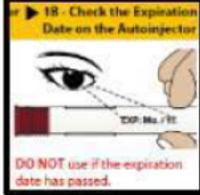
Observation/Measure	Risk	Trained Patients	Untrained Patients		Overall (N=45)
		Injection Naive (N=15)	Injection Naive (N=15)	Injection Experienced (N=15)	
Failure to Administer Full Dose	High	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Remove Cap	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Place Device at 90 Degree Angle	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Activate Device (Depress Needle Guard)	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Comprehend Need to Check Expiration Date (Step 1B)	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Comprehend Need to Inspect Fluid in Window (Step 1C)	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Comprehend Need to Confirm Dose (Step 4A)	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Identify Allowable Injection Site	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Remove Device From Packaging	Low	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)

8.2a Unaided Injection Findings – Performance Measures

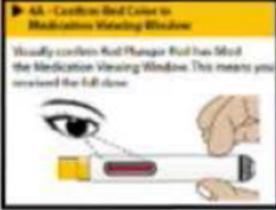
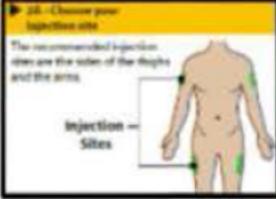
Observation/Measure	Risk	Trained Patients	Untrained Patients		Overall (N=45)
		Injection Naive (N=15)	Injection Naive (N=15)	Injection Experienced (N=15)	
Failure to Remove Device From Packaging	Low	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Remove Cap	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Place Device at 90 Degree Angle	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Activate Device (Depress Needle Guard)	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Hold Device Against Site For At Least One Second After Second Click	Low	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Administer Full Dose	High	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)

Observation/Measure	Risk	Trained Patients	Untrained Patients		Overall (N=45)
		Injection Naive (N=15)	Injection Naive (N=15)	Injection Experienced (N=15)	
Failure to Hold Device Against Site For At Least One Second After Second Click	Low	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Comprehend Need to Clean Injection Site (Step 2B)	Low	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Comprehend Need to Wait 5 Seconds After Delivery (Step 3B)	Low	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Comprehend Device Disposal (Step 4B)	Low	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)

8.3a Knowledge Probe and Reading Comprehension Performance

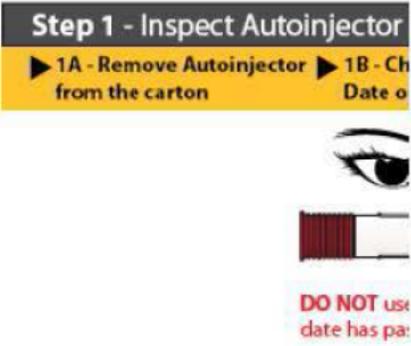
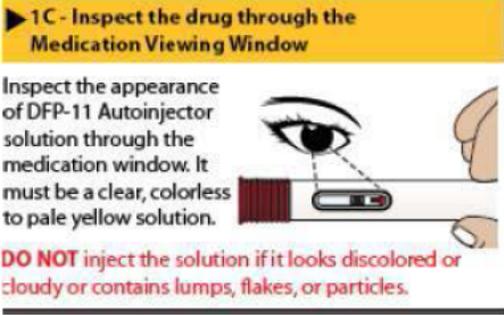
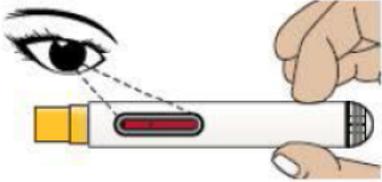
Observation/Measure	Risk	Trained Patients	Untrained Patients		Overall (N=45)
		Injection Naive (N=15)	Injection Naive (N=15)	Injection Experienced (N=15)	
Failure to Comprehend Need to Check Expiration Date (Step 1B) 	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Expressed Difficulty understanding this section of the IFU	N/A	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Comprehend Need to Inspect Fluid in Window (Step 1C) 	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Expressed Difficulty understanding this section of the IFU	N/A	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)

Observation/Measure	Risk	Trained Patients	Untrained Patients		Overall (N=45)
		Injection Naive (N=15)	Injection Naive (N=15)	Injection Experienced (N=15)	
<p>Failure to Comprehend Need to Clean Injection Site (Step 2B)</p> 	Low	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Expressed Difficulty understanding this section of the IFU	N/A	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
<p>Failure to Comprehend Need to Wait 5 Seconds After Delivery (Step 3B)</p> 	Low	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Expressed Difficulty understanding this section of the IFU	N/A	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)

Observation/Measure	Risk	Trained Patients	Untrained Patients		Overall (N=45)
		Injection Naive (N=15)	Injection Naive (N=15)	Injection Experienced (N=15)	
Failure to Comprehend Need to Confirm Dose (Step 4A) 	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Expressed Difficulty understanding this section of the IFU	N/A	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Comprehend Device Disposal (Step 4B) 	Low	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Expressed Difficulty understanding this section of the IFU	N/A	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Identify Allowable Injection Site 	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)

8.4b IAA IFU Recommendations

Overall the IFU performed very well. Users were able to comprehend and use the IFU effectively to successfully perform an unaided injection. Based on a review of user feedback, our domain knowledge, and experience with injection device IFUs we do not have any recommendations for critical changes to the IFU. However, we have minor recommendations to further enhance the IFU which are summarized in the table below.

Recommendation	IFU Illustration
<p>Add an illustration of removing the injector from the carton to the white space in step 1A</p>	
<p>Add the statement "It is normal to see an air bubble" to step 1C.</p>	
<p>Zoom in on medication viewing window in Step 4a more to clearly show plunger rod and (b) (4) stopper.</p>	<p>the Medication Viewing Window. This means you received the full dose.</p>  <p>CAUTION: Call your healthcare provider if the Red Plunger Rod has not filled the Medication Viewing Window.</p>

8.5a Opening Packaging and Removing Autoinjector

– Performance and Objective data

	Trained Patients	Untrained Patients		Overall (N=45)
	Injection Naive (N=15)	Injection Naive (N=15)	Injection Experienced (N=15)	
Successfully Opened Packaging	15/15 (100%)	15/15 (100%)	15/15 (100%)	45/45 (100%)
Successfully Removed Autoinjector	15/15 (100%)	15/15 (100%)	15/15 (100%)	45/45 (100%)
Showed No Difficulty Opening Carton	15/15 (100%)	14/15 (93%)	15/15 (100%)	44/45 (98%)
Showed No Difficulty Removing Device From Package	15/15 (100%)	15/15 (100%)	15/15 (100%)	45/45 (100%)

Summary of Potential Critical Task (High and Medium Risk) Failure Opportunities

Observation/Measure	Risk	Trained Patients	Untrained Patients		Overall (N=45)
		Injection Naive (N=15)	Injection Naive (N=15)	Injection Experienced (N=15)	
Failure to Administer Full Dose	High	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Remove Cap	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Place Device at 90 Degree Angle	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Activate Device (Depress Needle Guard)	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Comprehend Need to Check Expiration Date (Step 1B)	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Comprehend Need to Inspect Fluid in Window (Step 1C)	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Comprehend Need to Confirm Dose (Step 4A)	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Failure to Identify Allowable Injection Site	Medium	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/45 (0%)
Total		0/120 (0%)	0/120 (0%)	0/120 (0%)	0/360 (0%)

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On July 7, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: sumatriptan

D.2 Results

Our search did not identify cases, which described errors relevant to this review.

7 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/

JUSTINE HARRIS
10/09/2015

DANIELLE M HARRIS
10/09/2015

IRENE Z CHAN
10/13/2015

MEMORANDUM

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

DATE: September 15, 2015

TO: Director, Investigations Branch
ORA Los Angeles District Office
19701 Fairchild Road
Irvine, CA 92612

FROM: Charles R. Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **FY 2015, CDER High Priority Pre-Approval Data
Validation Inspection**, Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 208223

DRUG: DFP-11 (also known as DFN-11) Sumatriptan Succinate 3
mg/0.5 mL Injection

SPONSOR: Dr. Reddy's Laboratories, LPP, Andhra Pradesh, India

This inspection memo provides pertinent information to conduct the inspection of the clinical portion of the following bioavailability (BA) study. Background material is available in ECMS under the ORA folder. **The inspection should be completed and endorsed EIR submitted to CDER prior to November 30, 2015.**

Do not reveal the study to be inspected, drug names, or the study investigators to the site prior to the start of the inspection. The site will receive this information during the inspection opening meeting. The inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the OSIS POC.

Study Number: DFP-11/CD/002 [Celerion Project #: CA15826]

Study Title: "A Randomized Single-Dose, Three-Way Crossover Study to Determine the Relative Bioavailability

of DFP-11 Sumatriptan Succinate 3 mg/0.5 mL Injection versus Imitrex® Injection 3 mg/0.25 mL and 6 mg/0.5 mL (both using Imitrex® 6 mg/0.5 mL) Following Subcutaneous Injection in Healthy Adult Male and Female Subjects."

Clinical Site: Celerion
2420 West Baseline Road
Tempe, Arizona 85283
Tel: (602) 437-0097
Fax: (602) 437-3386

Investigator: Terry E. O'Reilly, MD

of Subjects: 36

Please bioequivalence studies performed at the sites (b) (4) The list should include information on test a (b) (4) samples retained at the site or at a third party for the bioequivalence studies. Please refer to **Table 1** at the end of **Section A** as an example.

SECTION A - RESERVE SAMPLES

Because study DFP-11/CD/002 is a bioavailability study and not a bioequivalence study, there is no regulatory requirement for retention of reserve samples. However, CDER review division has requested collection of reserve samples for study DFP-11/CD/002.

During the clinical site inspection, please:

- Verify that the site retained reserve samples. **Because there is no regulatory requirement, Form FDA 483 should not be issued if the site did not retain reserve samples for study DFP-11/CD/002.**
- If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific

studies, and that samples were stored under conditions specified in accompanying records.

- Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

TABLE 1

(b) (4)

SECTION B - CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Data Audit Checklist:

- Confirm that informed consent was obtained for all subjects enrolled at the site
- Audit the study records for all subjects enrolled at the site.
- Compare the study report submitted to FDA with the original documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
 - o Number of subject records reviewed during the inspection:_____
 - o Number of subjects screened at the site:_____

- o Number of subjects enrolled at the site:_____
- o Number of subjects completing the study:_____

- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- Confirm that adequate corrective actions were implemented for observations cited during the last inspection (if applicable).
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the OSIS POC prior to the inspection. Therefore, we request that the OSIS POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to the OSIS POC (see below). If it appears that the observations may warrant an OAI classification, notify the OSIS POC as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the OSIS POC.

OSIS POC: Yiyue Zhang, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Tel: (240) 402-6559
Fax: (301) 847-8748
E-mail: yiyue.zhang@fda.hhs.gov

The endorsed EIR should be sent to the following address:

Ms. Venese Dejernet
FDA/CDER/DBGLPC
WO51 RM5318 HFD-45
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
1-301-796-0650
venese.dejernet@fda.hhs.gov

Email cc:

ORA/PA-FO/LOS-DO/LOS-DIB/Maxwell
OSIS/Taylor/Dejernet/Fenty-Stewart/Nkah/Kadavil
OSIS/DNDBE/Bonapace/Dasgupta/Cho/Zhang
OSIS/DGDBE/Haidar/Skelly/Choi

Draft: YZ 9/11/2015, 9/15/2015
Edit: AD 9/15/2015, CB 9/15/2015
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/Celerion, Tempe, AZ

BE File#: 6960
FACTS: 11562622

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

/s/

YIYUE ZHANG
09/15/2015

ARINDAM DASGUPTA
09/15/2015

CHARLES R BONAPACE
09/15/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, and Ophthalmic

DATE: May 18, 2015

TO: Heimann, Martha R, Office of New Drug Products, WO21- 2546
Martha.Heimann@fda.hhs.gov
Bastings, Eric, Office of New Drug Products, WO22-4338
eric.bastings@fda.hhs.gov
Office of combination products at combination@fda.gov

RPM: Chen, Lana

Through: Dalal, Rakhi M., Ph.D., Toxicologist Respiratory, ENT, General Hospital and Ophthalmic (REGO) Devices Branch, Division of Manufacturing Quality (DMQ), Office of Compliance (OC), CDRH, WO66-3646

**Rakhi M.
Panguluri -S**

Digitally signed by Rakhi M. Panguluri -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300200210,
cn=Rakhi M. Panguluri -S
Date: 2015.06.01 10:28:35 -0400

From: Jamie Kamon-Brancazio, REGO, DMQ, OC, CDRH, OMPT. WO66-2627

Applicant: Dr. Reddy's Laboratories Limited
Survey Nos. 42, 45, 46 and 54
Bachupally, Qutubullapur
Ranga Reddy District, Telangana 500 072
India

FEI# 3002806664

US Agent: Hari Nagaradona, PhD
Senior Director/Head of Regulatory Affairs
Dr. Reddy's Laboratories, Inc.
Ph: 609-375-9042

Fax: 908-450-1469
Email: hnagaradona@drreddys.com

Application # NDA-208223
Consult # ICC1500183
Product Name: DFN-11 (sumatriptan injection)
Consult Evaluation of whether any of the facilities named in the submission should be evaluated or inspected for compliance with CGMPs for medical devices.
Instructions:
Documentation Review: Additional information required
Final Recommendation: Delayed Approval- Please see deficiencies on page 12

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA-208223.

PRODUCT DESCRIPTION

DFN-11 will be indicated for the acute treatment of migraine with or without aura in adults. DFN-11 Injection will be marketed as a prefilled, ready-to-use, single dose disposable auto-injector containing sumatriptan drug solution (3 mg/0.5 mL) in a pre-filled syringe (PFS) fully assembled into an auto-injector. The auto-injector consists of a single-use injector with the PFS driven by a plunger, in a preloaded state. The auto-injector device (secondary packaging) is a fixed single dose, disposable, drug delivery device. (b) (4)

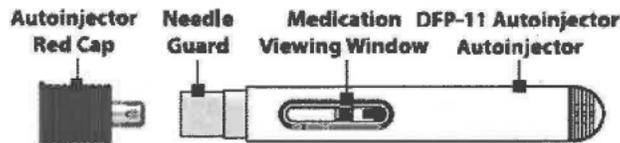


Table 2.3.P-11 Primary and Secondary Container/Closure Components

Container	Packaging Designation	Description
Syringe barrel	Primary	1 mL clear, USP Type I glass syringe
(b) (4) plunger closure	Primary	(b) (4)
Auto-injector	Secondary	Single-use, auto-injection device

REGULATORY HISTORY REVIEW

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

Inspection History Review:

Firm	Site (Address)	FEI#	Responsibility	Inspectional History & Conclusion-FACTS and/or TURBO
Dr. Reddy's Laboratories Limited	(b) (4)	(b) (4)	Applicant, (b) (4)	Abbreviated cGMP inspection conducted (b) (4) Inspection conclusion, NAI
Ajinomoto Althea Inc.	11040 Roselle Street San Diego, CA 92121	3004575449	Manufacture of pre-filled syringe, release and stability testing of DFN-11 Injection	Inspection conducted by CDER 01/26/2015-02/10/2015, Inspection conclusion, VAI (b) (4)
(b) (4)				

1. Dr. Reddy's Laboratories Limited

(b) (4)

Responsibility:

(b) (4)

An analysis of the firm's inspection history over the past (b) (4), showed that a drug inspection conducted on (b) (4) revealed no deficiencies and was classified NAI. This inspection was an abbreviated cGMP inspection giving coverage, according to the aforementioned compliance program, with an evaluation of the firm's Quality, Facilities and Equipment, Laboratory, Production, and Material Systems. The inspection included review of validations, written procedures, batch records, complaints, investigations and all other information pertinent to those systems. At the conclusion of the inspection, no deficiencies were noted that warranted an FDA 483 issuance - inspection was classified NAI. The previous FDA inspection at this location was a pre-approval inspection. The inspection was classified VAI, with multiple FDA 483 observations issued. At the close of current inspection, all previous FDA 483 observations appeared to have been addressed and corrected. The inspection report is not available at this time, however the endorsement text included enough information about the facility and the manufacture of the finished combination product to evaluate the facility's compliance with applicable 21 CFR part 820 regulations. No apparent issues related to 21 CFR part 820 were found.

2. Ajinomoto Althea Inc.

11040 Roselle Street

San Diego, CA 92121

Responsibility: Manufacture of pre-filled syringe, release and stability testing of

DFN-11 Injection

FEI# 3004575449

An analysis of the firm's inspection history over the past (b) (4), showed that a drug inspection conducted on (b) (4) revealed multiple deficiencies and was classified VAI. Some observations noted during the inspection could be considered

deficiencies under the Quality System Requirements, such as: issues related to the accuracy, sensitivity, specificity, and reproducibility of test methods have not been established and documented - The written stability program does not assure testing of the drug product in the same container-closure system as that which the drug products are marketed. - Equipment used in the manufacture, processing, packing, or holding of drug products is not appropriate design to facilitate operations for its intended use and cleaning and maintenance may all be related to requirements under 21CFR 820.30. The firm corrected the Quality System violations according to the endorsement text of the inspectional report. OC does not recommend an inspection at this time since the facility has been inspected within the last (b) (4), however a detailed review could not be completed at this time due to the unavailability of the most recent EIR.

3.

(b) (4)

There is no inspectional history for this firm. Therefore, an inspection is required for this firm.

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

According to the firm, manufacture, auto-injector assembly, components testing, release testing, and stability testing of the drug product are conducted for Dr. Reddy's Laboratories Ltd. by the firms listed below. The function of each firm is specified below.

- 1) Manufacture of pre-filled syringe, release and stability testing (other than specified for other contractors) of DFN-11 Injection is performed by Ajinomoto Althea Inc., San Diego, CA.
- 2) Raw material identification testing for sumatriptan succinate by (b) (4) is performed by (b) (4).
- 3) Stability storage of DFN-11 injection is performed by Ajinomoto Althea Inc., San Diego, CA (b) (4).
- 4) Final product release and stability testing for particulate matter, endotoxins content and sterility are performed by (b) (4).

5) Container closure integrity testing for pre-filled syringes is performed by (b) (4)

6) Manufacture of auto-injector components and sub-assemblies is performed by (b) (4). Auto-injector assembly, packaging and labeling are performed by (b) (4).

There does not appear to be any information about how Dr. Reddy's Laboratories Ltd. controls all firms involved in the manufacturing to ensure it is designed and produced in accordance with the applicable Quality Systems requirements. There also does not appear to be any description of how Dr. Reddy's Laboratories Ltd. will ensure that the quality policy is understood, implemented, and maintained at all levels of the organization.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

3.2.P.7.2 Syringe Barrel-3.2.P.7.2.1 Description

(b) (4)

The following DMFs are referenced for the syringe barrel and the LOAs for the DMFs:

(b) (4)

3.2.P.7.3 (b) (4) Plunger-3.2.P.7.3.1 Description

(b) (4)

(b) (4)

The following DMFs are referenced for the (b) (4) plunger and LOAs:

(b) (4)

3.2.P.7.4 Autoinjector-3.2.P.7.4.1 Description of Autoinjector

The D FN-11 auto-injector (Figure 3.2.P.7-1) is a fixed single dose, disposable, (b) (4)

(b) (4) device (b) (4)

(b) (4)

(b) (4) The final design has met all Design Input requirements as evidenced by the successful Design Verification and Validation Testing.

(b) (4)

3.2.P.7.4.1.2 Pre-filled Syringe (PFS)

(b) (4) (b) (4) 1.0 mL pre-filled USP Type I glass syringe with 29 gauge thin wall and ½

inch long staked needle and Rigid Needle Shield (RNS), containing 0.5mL sterile solution of sumatriptan succinate.

(b) (4)

The following Device Master File is referenced for the auto-injector and the LOA:

- (b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

(b) (4)

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

The firm did not appear to provide a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System. The CAPA system should require analysis of sources of quality data to identify existing and potential cause of nonconforming practices and products; investigation of the cause of nonconformities, identification of actions needed to correct and prevent recurrence of non-conformances; and, verification or validation of the actions.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170

Installation is not required for this combination product.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product.

MANUFACTURING

Production and Process Controls

(b) (4)



(b) (4)

Acceptance Activities

The firm provided the specifications for the combination product, including the test method and acceptance criteria for the injectability of the finished product. Please find acceptance criteria for this combination product listed on the tables below and in the Design Controls section of this memo for individual components.

The process controls and acceptance limits are listed in Table 3.2.P.3.3-5 for the manufacture of the pre-filled syringes.

(b) (4)



(b) (4)

(b) (4)

(b) (4)

Documentation Review Recommendation

This application is overall deficient. Additional information is needed for a complete documentation review.

Deficiencies to be conveyed to the applicant

The following deficiencies have been identified during the documentation review of application for DFN-11 (sumatriptan injection), NDA-208223, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

1. Per the application, several firms are involved in the manufacturing of finished combination product. However, the firm did not describe the organizational structure (i.e. organization structure chart) and explain how it controls all levels of the structure (i.e. agreements). Please provide a complete summary that adequately addresses the requirements of 21 CFR 820.20, Management Control.
2. Per the application, multiple materials including device constituent components and parts, and other services will be provided by external suppliers. However, the firm did not describe the purchasing control process covering supplier evaluation, record maintenance of acceptable suppliers, and method to assure that changes made by contractors/suppliers will not affect the final combination product through acceptance activities and supplier agreements. The firm did not explain how it applied its purchasing controls to the suppliers/contractors involved in the manufacturing of the combination product. Please provide a complete summary that adequately addresses the requirements of 21 CFR 820.50, Purchasing Controls.
3. The firm did not provide any information pertaining to its Corrective and Preventive Action (CAPA) System. The CAPA system should require analysis of sources of quality data to identify existing and potential cause of nonconforming practices and products; investigation of the cause of nonconformities, identification of actions needed to correct and prevent recurrence of non-conformances; and, verification or validation of the actions. Please provide a complete summary that adequately addresses the requirements of 21 CFR 820.100.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of application NDA-208223 and has the following recommendations:

The approvability of application DFN-11 (sumatriptan injection)-NDA-208223 should be delayed for the following reasons:

- (1) Deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review. The NDA-208223 approvability under the Medical Device Regulations should be delayed until the applicant provides the additional information requested and an adequate documentation review of the application has been completed.
- (2) A pre-approval inspection is recommended for the following facility. No inspection history of the stated firm could be identified.

(b) (4)
- (3) Establishment Inspection Reports (EIR) for Dr. Reddy's Laboratories Ltd. Hyderabad, AP, IN and Ajinomoto Althea Inc. are not available at this time, however Inspection recommendations can be updated throughout the review cycle as deemed necessary.
- (4) Review of the performance, bio-compatibility and engineering of the finished combination product is deferred to CDRH/ODE.

Jamie Kamon-brancazio -S
2015.05.20 21:17:20 -04'00'

Jamie Kamon-Brancazio

Prepared: JKamon-Brancazio: 05/18/2015

Reviewed: FMLast name: Month/Day/Year

CTS No.: ICC1500183

NDA-208223

Review Cycle Meeting Attendance:

Month/Day/Year

Month/Day/Year

Month/Day/Year

Inspectional Guidance

Firm to be inspected:



FEI: None on file

CDRH recommends the inspection under the applicable Medical Device Regulations of (b) (4):

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the DFN-11 (sumatriptan injection)(NDA-208223).

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Jamie Kamon-Brancazio
Consumer Safety Officer
Respiratory, ENT, General Hospital, Ophthalmic (REGO)
Division of Manufacturing and Quality (DMQ)
Office of Compliance, WO66 -2627
Phone: 301-796-3187

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Francisco Vicenty

Chief

REGO

DMQ

Office of Compliance, WO66 -2642

Phone: 301-796- 5577

**THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM
DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL
INFORMATION**