CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208025Orig1s000

OTHER REVIEW(S)

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: 11/10/2015

TO: Division of Nonprescription Drug Products
Office of Drug Evluation IV

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208025

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Clinical	inVentiv Health Clinique	2500 Rue Einstein, Quebec City, Quebec, Canada

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: 11/4/2015

TO: Division of Nonprescription Drug Products
Office of Drug Evluation IV

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208025

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

Although the last inspection was classified as a VAI, based on the nature of the findings from the last inspection, and our recommendation to the review division, an inspection of the site will not be needed at this time.

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

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

/s/

SHILA S NKAH
11/10/2015

Labeling Review for Lansoprazole Delayed-Release Orally Disintegrating Tablets

Draft Labeling

SUBMISSION DATES:	May 11, 2016 May 16, 2016 May 20, 2016 May 24, 2016 May 25, 2016
NDA/SUBMISSION TYPE:	208025
ACTIVE INGREDIENTS:	Lansoprazole, 15 mg
DOSAGE FORM	Delayed-release orally disintegrating tablet
SPONSOR:	Dexcel Pharma Technologies, Ltd. U.S. Agent: Camargo Pharmaceutical Services, LLC Ruth E. Stevens, Ph.D., M.B.A. Chief Scientific Officer, Executive Vice President 513-618-0341
REVIEWER:	Mary R. Vienna, RN, MHA, DNDP, ODE IV
ASSOCIATE DIRECTOR For LABELING	Ruth E. Scroggs, PharmD, DNDP, ODE IV
REGULATORY PROJECT MANAGER	Alina Salvatore, RPh, MS, Project Manager, DNDP, ODE IV

I. BACKGROUND

Dexcel Pharma Technologies, Ltd. (Dexcel) and its agent, Camargo Pharmaceutical Services, LLC, submitted on December 8, 2014, an original new drug application (NDA) 208025, under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act (FD&C Act). The sponsor proposes to market a strawberry-flavored delayed-release orally disintegrating tablet form of the proton pump inhibitor (PPI) lansoprazole 15 mg as an over-the-counter (OTC) drug product for

the treatment of frequent heartburn (occurring 2 or more times per week) in adults 18 years of age and older. The delayed-release capsule form of lansoprazole 15 mg is currently approved as an OTC drug product in NDA 022327 (Prevacid 24HR), and is the reference listed drug (RLD) for this application.

The April 25, 2016 labeling review discusses the December 8, 2014, August 6, 2015, and March 10 and March 21, 2016 labeling submissions, and includes labeling recommendations that were communicated to the sponsor on May 5, 2016. This review, the second of two, amends the April 25, 2016 labeling review. This is a review of the labeling submitted May 11, 16, 20 and 24, 2016, compared to the labeling reviewed on April 25, 2016.

An information request with labeling comments was sent to the sponsor on May 5, 2016. The sponsor responded on May 11, 2016 with revised labeling. The May 11, 2016, submission withdrew the 7-count immediate container (blister), but also stated that such blisters had been approved in the past for other PPIs. Further review found this to be correct, and an information request was sent to the sponsor on May 18, 2016, requesting re-submission of the 7-count blister label (b) (4) Revisions to the Drug Facts label for the 14-, 28- and 42-count cartons, 42-count bottle and 42-count bottle with window cartons were also requested, as the bullets were formatted incorrectly. The sponsor submitted revised labeling on May 20, 2016, and a teleconference was held on May 23, 2106 to clarify the submission contents, which proposed a new PDP design for cartons containing the 7-count blisters. The (b) (4) 7-count blisters would be packaged in the same size cartons as the 14-count blisters.

Submitted Labeling	Representative of Following SKUs	Submission date/replaces
7-count immediate container (blister)	N/A	August 6, 2015 Withdrawn May 11, 2016 May 20, 2016
14-count immediate container (blister)	N/A	December 8, 2014 Revised August 6, 2015
14-count immediate container (bottle)	N/A	December 8, 2014 Revised August 6, 2015 Revised May 16, 2016
14-count inner carton (blister)	N/A	August 6, 2015 Revised May 11, 2016 Revised May 20, 2016
14-count inner carton (blister)		May 20, 2016 (b) (4)

Submitted Labeling	Representative of Following SKUs	Submission date/replaces
14-count carton (blister)	N/A	December 8, 2014 Revised August 6, 2015 Revised May 11, 2016 Revised May 20, 2016
14-count carton (blister)		May 20, 2016
(b) (4)		
14-count carton (bottle)	N/A	December 8, 2014 Revised August 6, 2015 Revised May 11, 2016
14-count carton with window (bottle)	N/A	August 6, 2015 Revised May 11, 2016
28-count carton (blister)	N/A	December 8, 2014 Revised August 6, 2015 Revised May 11, 2016 Revised May 20, 2016
28-count carton (bottle)	N/A	December 8, 2014 Revised August 6, 2015 Revised May 11, 2016
28-count carton with window (bottle)	N/A	August 6, 2015 Revised May 11, 2016
42-count carton (blister)	N/A	December 8, 2014 Revised August 6, 2015 Revised May 11, 2016 Revised May 20, 2016
42-count carton (bottle)	N/A	December 8, 2014 Revised August 6, 2015 Revised May 11, 2016 Revised May 20, 2016
42-count carton with window (bottle)	N/A	August 6, 2015 Revised May 11, 2016 Revised May 20, 2016
Consumer Information Leaflet	N/A	August 6, 2015 Revised May 11, 2016

II. REVIEWER'S COMMENTS

A. 14-count inner carton, 14-, 28- and 42-count cartons

i. Outer Carton Label Outside Drug Facts

Principal Display Panel

a. The font size of "Lansoprazole" is increased and the font size of "Delayed Release Orally Disintegrating Tablets 15 mg" is slightly reduced, which serves to increase the prominence of the proprietary/established name. The entire name is changed to lower case letters.

Comment: This is acceptable.

b. The statement (b) (4) is removed from the carton.

Comment: This is acceptable.

c. The approved statement "Keep the carton and package insert. They contain important information." appears on the top flap of the carton labels.

Comment: This is acceptable.

i. Outer Carton Drug Facts Label

a. ***Directions***

1. Under the heading "**14-Day Course of Treatment**", the bullets have been revised to state:

- take 1 tablet before eating in the morning
- **do not crush or chew tablet**
- place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water
- take every day for 14 days
- do not take more than 1 tablet a day
- do not use for more than 14 days unless directed by your doctor
- do not take this medicine with alcohol

Comment: This reflects the labeling comments of the Medical Officer review of May 4, 2016, and is acceptable.

2. The last bullet in the Directions section states:

- Children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition.

The first word begins with an upper case letter "C" instead of a lower case "c":

Comment: The content is acceptable. Request that the sponsor change the uppercase "C" to a lowercase "c" as a minor editorial revision, to be submitted in final printed labeling.

b. ***Questions?***

"***Questions?***" has been changed to read "***Questions or comments?***" and the telephone number 1-800-719-9260 has been added. In the May 11, 2016 submission, the sponsor commits to include the time that the toll-free number is in operation at the time of final printed labeling.

Comment: This is acceptable.

c. **Other Sections/Issues**

- The barline is placed between the warning "**Stop use and ask a doctor if**" and the pregnancy/breastfeeding warning, and the graphic arrow placement and the location of the ***Questions?*** section complies with 201.66(d).

Comment: This is acceptable.

B. 14-, 28- and 42-count bottle cartons and bottle cartons with window

i. Outer Carton Label Outside Drug Facts

Principal Display Panel

a. The font size of "Lansoprazole" is increased and the font size of "Delayed Release Orally Disintegrating Tablets 15 mg" is slightly reduced, which serves to increase the prominence of the proprietary/established name. The entire name is changed to lower case letters.

Comment: This is acceptable.

b. The established name "Lansoprazole" appears on the 14-count bottle carton and bottle carton with window labels when printed.

Comment: This is acceptable.

c. The two bulleted statements below the statement of identity are removed on the 14-, 28- and 42-count bottle cartons with window, which serves to increase the prominence of the statement of identity and the declaration of net quantity of contents.

Comment: This is acceptable.

d. The statement (b) (4) is removed from the carton.

Comment: This is acceptable.

ii. Outer Carton Drug Facts Label

See Section II.A.ii.a-b

Other Sections/Issues

- The ***Other Information*** and ***Inactive Ingredients*** sections of the Drug Facts label are listed in the required order, and the graphic arrow placement and the location of the last Drug Facts information complies with 201.66(d).

Comment: This is acceptable.

iii. Immediate Container Labels:

a. **7-count blister**

The sponsor withdrew the 7-count blister label on May 11, 2016 in response to our comments, but also stated in the submission that 7-count blisters had been approved in the past. Upon further review, the sponsor is correct that a 7-count blister was approved for Prilosec OTC (NDA 21-229) and Omeprazole (NDA 22-032) with NDA approval, and that labeling was subsequently changed to a 14-count blister. The sponsor re-submitted a 7-count blister card on May 20, 2016, and submitted a clarification that the 7-count blister card is to be marketed in the same size carton as the 14-count blister card on May 25, 2016.

Comment: This is acceptable.

iv. Consumer Information Leaflet

a. The font size of “Lansoprazole” is increased and the font size of “Delayed Release Orally Disintegrating Tablets 15 mg” is slightly reduced, which serves to increase the prominence of the proprietary/established name. The entire name is changed to lower case letters.

Comment: This is acceptable.

b. The bullet under the "acid reducer" statement has been revised from:
   - May take 1 to 4 days for full effect, although some people get complete (b) (4) within 24 hours

   to:
   - May take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours

   in order to align with the approved statement of the RLD.

Comment: This is acceptable.

c. Under the heading "**How to Take Lansoprazole delayed release orally disintegrating tablets 14-DAY Course of treatment**", the following bullets state:
   - take 1 tablet before eating in the morning
   - **do not crush or chew tablet**
   - place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water
   - take every day for 14 days
   - do not take more than 1 tablet a day
   - do not use for more than 14 days unless directed by your doctor
   - do not take this medicine with alcohol

   Comment: This reflects the labeling comments of the Medical Officer review of May 4, 2016, and is acceptable.

d. Under the heading "**For Questions or Comments About Lansoprazole delayed release orally disintegrating tablets**", the telephone number 1-800-719-9260 has been added. The sponsor commits to include the time that the toll-free number is in operation at the time of final printed labeling.

   Comment: This is acceptable.

II. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Lansoprazole delayed release orally disintegrating tablet labeling and request final printed labeling with the minor editorial revisions to the ***Drug Facts*** label listed below:

1. Under the ***Directions*** section, change the letter "C" of the first word of the last bullet, "children", from an upper case letter "C" to a lower case "c" to read:
   - children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition.

2. Under the "***Questions or comments?***" section, include the time the toll-free number is in operation as committed to in the May 11, 2016, submission.

Final printed labeling (FPL) must include the revisions listed and be otherwise identical to the 14-count immediate container (blister) label submitted on August 6, 2015; the 14-count bottle carton and bottle carton with window, the 28-count bottle carton and bottle carton with window labels, and the Consumer Information Leaflet submitted on May 11, 2016; the 14-count immediate container (bottle) label submitted on May 16, 2016; and the 7-count immediate container (blister), the 14-count inner blister carton, the 14-, 28- and 42-count blister cartons, and the 42-count bottle carton and bottle carton with window labels submitted on May 20, 2016.

In the approval letter, remind the sponsor of the following:

We remind you that, if you should be interested in marketing other package configurations in the future (e.g. bottles containing greater than 14 capsules, package sizes greater than 42-count), we will expect submission of a prior approval supplement that includes data to adequately demonstrate appropriate consumer comprehension of limitations of use. You are encouraged to contact the Division of Nonprescription Drug Products about the content and format of such a supplement prior to submission.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and were evaluated in this labeling review:

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

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

/s/

MARY R VIENNA
06/02/2016

RUTH E SCROGGS
06/03/2016

505(b)(2) ASSESSMENT

Application Information		
NDA # 208025	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: None requested by the sponsor Established/Proper Name: lansoprazole Dosage Form: delayed-release, orally disintegrating tablet Strengths: 15 mg once daily		
Applicant: Dexcel Pharma Technologies Agent for Applicant: Camargo Pharmaceutical Services, LLC		
Date of Receipt: August 7, 2015		
PDUFA Goal Date: June 7, 2016	Action Goal Date (if different):	
RPM: Alina Salvatore		
Proposed Indication(s): Treatment of frequent heartburn (occurring 2 or more days a week) in adults age 18 years and older		

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 022327 Prevacid 24HR	FDA's previous finding of safety and efficacy
Published literature	

*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 literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

The sponsor has conducted a bioequivalence study and a comparative bioavailability study (food effect) to provide the scientific bridge to the agency's finding of safety and efficacy for Prevacid 24HR.

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).*

Prevacid 24HR (NDA 022327)

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

YES ☐ NO ☐

[1]For 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)
Prevacid 24HR	022327	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 change in dosage form, from a DR capsule (Prevacid 24HR) to a DR orally disintegrating tablet.

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 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):

- Prevacid (lansoprazole) delayed-release orally disintegrating tablets 15mg (NDA 21428)

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):
NDA 022327 Prevacid 24HR (lansoprazole) delayed-release capsule, 15mg – same indication and referenced as the listed drug

NDA 020406 Prevacid (lansoprazole) delayed-release capsule, 30mg and 15mg – different indications (for Rx use) and not referenced as a listed drug

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s):

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):
Expiry Date:

☐ 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 ☐

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

/s/

ALINA W SALVATORE
05/12/2016

Labeling Review for Lansoprazole Delayed-Release Orally Disintegrating Tablets

Draft Labeling

SUBMISSION DATES:	December 8, 2014 August 6, 2015 March 10, 2016 March 21, 2016
NDA/SUBMISSION TYPE:	208025
ACTIVE INGREDIENTS:	Lansoprazole, 15 mg
DOSAGE FORM	Delayed-release orally disintegrating tablet
SPONSOR:	Dexcel Pharma Technologies, Ltd. U.S. Agent: Camargo Pharmaceutical Services, LLC Ruth E. Stevens, Ph.D., M.B.A. Chief Scientific Officer, Executive Vice President 513-618-0341
REVIEWER:	Mary R. Vienna, RN, MHA, DNDP, ODE IV
ASSOCIATE DIRECTOR For LABELING	Ruth E. Scroggs, PharmD, DNDP, ODE IV
REGULATORY PROJECT MANAGER	Alina Salvatore, Project Manager, DNDP, ODE IV

I. BACKGROUND

Dexcel Pharma Technologies, Ltd. (Dexcel) and its agent, Camargo Pharmaceutical Services, LLC, submitted on December 8, 2014, an original new drug application (NDA) 208025, under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act (FD&C Act). The sponsor proposes to market a strawberry-flavored delayed-release orally disintegrating tablet form of the proton pump inhibitor (PPI) lansoprazole 15 mg as an over-the-counter (OTC) drug product for the treatment of frequent heartburn (occurring 2 or more times per week) in adults 18 years of

age and older. The delayed-release capsule form of lansoprazole 15 mg is currently approved as an OTC drug product in NDA 022327 (Prevacid 24HR), and is the reference listed drug (RLD) for this application.

A review by the Division of Medication Error Prevention and Analysis (DMEPA) was completed on April 22, 2016, and the comments are addressed in this review.

The December 8, 2014 submission resulted in a Refusal To File (RTF) action on February 6, 2015, and the RTF letter requested revised labeling to include font specifications for the Drug Facts label, the submission of a proposed consumer information leaflet (CIL) and a 14-count inner carton label. Dexcel submitted its response to the RTF action on August 6, 2015, which included the requested revisions and labels in a different design than had been proposed in the original submission and examples discussed at the RTF meeting on April 13, 2015. The sponsor also submitted new additional labeling to include a 7-count immediate container (blister) and 14-, 28-, and 42-ct bottle cartons with a window configuration.

An information request was sent to the sponsor on March 3, 2016, requesting clarification on the intended use for the 7-count immediate container (blister). The sponsor responded on March 10, 2016 with the clarification that the 7-count blister is to be used with the 14-count carton package, which will contain two 7-count blisters. A second information request was sent to the sponsor on March 15, 2016, requesting samples of the tablet and cartons to verify the "Actual size" claim on the Principal Display panel (PDP). The sponsor responded on March 21, 2016, with samples of the tablets and cartons, and a description of the process for ensuring the "actual size" claim on the label will be controlled for accuracy.

The submitted labeling is compared to the most recently approved labeling of the RLD for this application, Prevacid 24HR delayed-release capsules, 15 mg (NDA 022327, S-022).

Submitted Labeling	Representative of Following SKUs	Submission date/replaces
7-count immediate container (blister)	N/A	August 6, 2015
14-count immediate container (blister)	N/A	December 8, 2014 Revised August 6, 2015
14-count immediate container (bottle)	N/A	December 8, 2014 Revised August 6, 2015
14-count inner carton (blister)	N/A	August 6, 2015
14-count carton (blister)	N/A	December 8, 2014 Revised August 6, 2015
14-count carton (bottle)	N/A	December 8, 2014 Revised August 6, 2015

Submitted Labeling	Representative of Following SKUs	Submission date/replaces
14-count carton with window (bottle)	N/A	August 6, 2015
28-count carton (blister)	N/A	December 8, 2014 Revised August 6, 2015
28-count carton (bottle)	N/A	December 8, 2014 Revised August 6, 2015
28-count carton with window (bottle)	N/A	August 6, 2015
42-count carton (blister)	N/A	December 8, 2014 Revised August 6, 2015
42-count carton (bottle)	N/A	December 8, 2014 Revised August 6, 2015
42-count carton with window (bottle)	N/A	August 6, 2015
Consumer Information Leaflet	N/A	August 6, 2015

II. REVIEWER'S COMMENTS

A. 14-count inner carton, 14-, 28- and 42-count cartons

i. Outer Carton Label Outside Drug Facts

Principal Display Panel

a. The background of the principal display panel (PDP) is purple, and the established name "LANSOPRAZOLE" appears in white font at the top of the PDP. The established name also serves as the proprietary name, as no proprietary name has been submitted for review. The dosage form and dose "DELAYED RELEASE ORALLY DISINTEGRATING TABLETS 15 mg" appears below it in identical font, which serves to decrease the prominence of the proprietary/established name. The pharmaceutical category ACID REDUCER completes the statement of identity in significantly smaller font. Because the established name, lansoprazole, will be the name marketed to the consumer, the result is that as currently proposed, the other text competes for the consumer's attention on the PDP and may be confusing.

Comment: This is not acceptable. Because the established name will be the name marketed to the consumer, the result is that as currently proposed, the other text competes for the consumer's attention on the PDP and may be confusing. Therefore, increase the relative prominence of the established name (nonproprietary name), lansoprazole, consistent with the PDP design of the

proposed labeling submitted on December 8, 2014, and discussed at the April 13, 2015 meeting between FDA and Dexcel.

b. Two bulleted statements appear below the statement of identity:
   - May take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours
   - Clinically Proven to Treat Frequent Heartburn

Comment: These statements appear on the approved PDP of the reference listed drug (RLD) and are acceptable.

c. The declaration of net quantity of contents appears at the lower left corner of the PDP.

Comment: This is acceptable.

d. For the 14-count carton label, the statement "One 14-day course of treatment" appears underneath the declaration of net quantity. For the 28-count carton label, the statement "Two 14-day courses of treatment" appears underneath the declaration of net quantity. For the 42-count carton label, the statement "Three 14-day courses of treatment" appears underneath the declaration of net quantity.

Comment: These statements appear on the approved PDP of the RLD and are acceptable.

e. An image of the tablet appears in the lower right corner of the PDP with the claim "Actual size" to the left of the tablet. In response to our March 14, 2016, communication requesting tablets and cartons of the to-be-marketed product, the sponsor submitted three tablets on March 20, 2016. These were compared to the image on the 14-ct model blister and bottle carton.

Comment: The proposed tablet image represents a true depiction of the actual tablet in regards to tablet imprint, size and color, and is therefore acceptable.

f. The statement [redacted] (b) (4) he statement "May take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours" is located close by on the PDP, [redacted] (b) (4). Refer to DMEPA labeling review of April 22, 2016.

Comment: This is not acceptable. Remove [redacted] (b) (4) **that is located adjacent to the tablet image,** [redacted] (b) (4) **earby statement "May take 1 to 4 days for**

full effect, although some people get complete relief of symptoms within 24 hours", (b) (4)

g. The tamper-evident feature statement "Safety Feature – Do not use if printed tablet blister unit is open or torn." appears on the top flap of the carton.

Comment: This is acceptable.

h. The RLD labeling has the approved statement "Keep the carton and package insert. They contain important information." on the carton labels, and the proposed bottle carton labeling also includes this statement. This is missing from the proposed blister carton labels.

Comment: This is not acceptable. Add the statement "Keep the carton and package insert. They contain important information" to the blister carton labels. This is approved labeling for the RLD.

i. The left side panel of the 14-count inner and outer carton, and the top flap of the 28- and 42-count cartons contain the manufacturing information:

Manufactured by:
Dexcel Pharma Technologies Ltd.
10 Hakidma St. Yokneam 2069200, Israel

Comment: This complies with 21 CFR 201.1 and is acceptable.

j. The top flap of the 14-count inner carton contains the statement "NOT FOR RESALE".

Comment: This is acceptable.

i. Outer Carton Drug Facts Label

The Drug Facts Label (DFL) is identical to the reference listed drug (RLD) except as follows:

a. ***Active ingredient (in each tablet)***: "lansoprazole 15 mg"

Comment: The dosage form has been changed to reflect the difference from the RLD and is acceptable.

b. (b) (4)

Keep out of reach of children:

"**Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away (1-800-222-1222)"

Comment: The Poison Control Center phone number has been added to the statement and is acceptable.

c. ***Directions***

1. Under the heading "**14-Day Course of Treatment**", the following bullets state:

- take 1 tablet before eating in the morning. Place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water.
- take every day for 14 days
- do not take more than 1 tablet a day
- do not crush or chew tablets
- do not use for more than 14 days unless directed by your doctor

The RLD directions on how to take the drug are contained in the fourth bullet "[bullet] Swallow whole. Do not crush or chew tablets." The proposed labeling moves the "Swallow whole" instruction to the first bullet and adds instructions on how to take the orally disintegrating tablet form. It also combines these statements with the instructions on the timing of the dose "Take 1 tablet before eating in the morning.", creating a long bullet that is conceptually very complex.

Comment: This is not acceptable. Create a separate bullet that only contains instructions on how to take the tablet, so that the section reads:

- **take 1 tablet before eating in the morning**
- **place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water.**
- **take every day for 14 days**
- **do not take more than 1 tablet a day**
- **do not crush or chew tablets**
- **do not use for more than 14 days unless directed by your doctor**

See Clinical Review for additional rationale.

The last bullet under the heading states:

- do not take this medicine with alcohol

Comment: As per the Clin/Pharm review, the alcohol dose dumping study supports this additional instruction. This is acceptable.

2. The last bullet in the Directions section states:

   - "children under 18 years of age: ask a doctor. Heartburn in children may sometimes be caused by a serious condition".

     The RLD directions state "children under 18 years of age: ask a doctor *before use* (italics added for this review)."

Comment: This is not acceptable. Revise the statement to be identical to the RLD "[bullet] children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition"

d. ***Inactive ingredients***
The inactive ingredients are listed in alphabetical order in compliance with 21 CFR 201.66(c)(8).

Comment: This is acceptable. Refer to CMC review regarding acceptability of inactive ingredients.

e. ***Questions?***
1-800-XXX-XXXX

Comment: This is not acceptable. Replace the placeholder Xs with an actual telephone number. 21 CFR 201.66(c)(9) requires that this section contain a telephone number of a source to answer questions about the product. We also recommend that the label include the days of the week and times that the toll-free number is in operation.

f. **Other Sections/Issues**
The Drug Facts label does not comply with the specifications of 21CFR 201.66(d) in the following ways:

- There is a missing barline between the warning "**Stop use and ask a doctor if**" and the pregnancy/breastfeeding warning as required in 21 CFR 201.66(d)(5).
- For the 14-count inner and outer carton:
  - the visual graphic arrow on the Inactive Ingredient panel does not properly signal the continuation of the Drug Facts label to the next adjacent panel as required in 21 CFR 201.66(d)(5).
  - The ***Questions?*** Section of the Drug Facts label appears in isolation at the top flap of the carton, and does not comply with 21 CFR 201.66(d)(7).

Comment: This is not acceptable. Place a barline between the "Stop use and ask a doctor if" and the pregnancy/breastfeeding warning as required in 21 CFR 201.66(d)(5). For the 14-count cartons, reformat the visual graphic arrows on the Drug Facts label to properly signal the continuation of the Drug Facts label, and properly format the *Questions?* section of the Drug Facts label to comply with 21 CFR 201.66(d)(5) and 201.66(d)(7).

B. 14-, 28- and 42-count bottle cartons and bottle cartons with window

The bottle cartons come in two configurations. The 14-, 28- and 42-count bottle cartons are enclosed on all sides, and the 14-, 28- and 42-count bottle cartons with window have the upper half of the PDP section cut away to expose the bottle.

i. Outer Carton Label Outside Drug Facts

Principal Display Panel

a. The background of the PDP is purple, and the established name "LANSOPRAZOLE" appears in white font at the top of the PDP. The established name also serves as the proprietary name, as discussed in the Background section of this review. The dosage form and dose "DELAYED RELEASE ORALLY DISINTEGRATING TABLETS 15 mg" appears below it in identical font, which serves to decrease the prominence of the proprietary/established name. The pharmaceutical category ACID REDUCER completes the statement of identity in significantly smaller font. Because the established name, lansoprazole, will be the name marketed to the consumer, the result is that as currently proposed, the other text competes for the consumer's attention on the PDP and may be confusing.

Comment: This is not acceptable. Because the established name will be the name marketed to the consumer, the result is that as currently proposed, the other text competes for the consumer's attention on the PDP and may be confusing. Therefore, increase the relative prominence of the established name (nonproprietary name), lansoprazole, consistent with the PDP design of the proposed labeling submitted on December 8, 2014, and discussed at the April 13, 2015 meeting between FDA and Dexcel.

b. The established name "LANSOPRAZOLE" does not appear on the 14-count bottle carton and bottle carton with window labels when printed, although it appears on the label when viewed electronically.

Comment: This is not acceptable. Submit 14-count bottle carton labeling that displays the established name when printed.

c. Two bulleted statements appear below the statement of identity:
   - May take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours
   - Clinically Proven to Treat Frequent Heartburn

   On the 14-, 28- and 42-count bottle carton with window, the entire PDP design is shifted to the bottom half of the carton. The inclusion of these bullets, which are not required, serves to decrease the prominence of required items such as the statement of identity and the declaration of net quantity of contents.

   Comment: These statements are not acceptable for use with the bottle carton with window design. The window design serves to shift the entire PDP to the bottom half of the carton. With half as much area, the additional text affects the prominence of required items such as the statement of identity and the declaration of net quantity of contents. 21 CFR 201.15(a)(4) and 201.15(a)(6) state that required statements can lack the required prominence by reason of "…use of label space for any word, statement, design, or device which is not required by or under authority of the act to appear on the label;" and "…crowding with other written, printed or graphic matter". The two bulleted statements are not required labeling on the PDP, and should be removed from the PDP of the bottle cartons with windows

d. The declaration of net quantity of contents appears at the lower left corner of the PDP.

   Comment: This is acceptable.

e. For the 14-count carton label, the statement "One 14-day course of treatment" appears underneath the declaration of net quantity. For the 28-count carton label, the statement "Two 14-day courses of treatment" appears underneath the declaration of net quantity. For the 42-count carton label, the statement "Three 14-day courses of treatment" appears underneath the declaration of net quantity.

   Comment: These statements appear on the PDP of the RLD and are acceptable.

f. An image of the tablet appears in the lower right corner of the PDP with the claim "Actual size" to the left of the tablet. In response to our March 14, 2016, communication requesting tablets and cartons of the to-be-marketed product, the sponsor submitted three tablets on March 20, 2016. These were compared to the image on the 14-ct model blister and bottle carton.

   Comment: The proposed tablet image represents a true depiction of the actual tablet in regards to tablet imprint, size and color, and is therefore acceptable.

g. The statement [redacted] The statement "May take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours" is located close by on the PDP, [redacted] Refer to DMEPA labeling review of April 22, 2016.

Comment: This is not acceptable. Remove [redacted] that is located adjacent to the tablet [redacted] statement "May take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours", [redacted]

h. For the 14-count carton labels, the statement "1 bottle inside" appears in the upper right corner of the PDP. This statement is replaced with "2 bottles inside" for the 28-count carton labels, and "3 bottles inside" for the 42-count carton labels.

Comment: These statements appear on the RLD labeling and are acceptable.

i. The tamper-evident feature statement "Safety Feature – Do not use if printed seal under cap is broken or missing." appears on the top flap of the 14-count cartons and on the right side flap of the 28- and 42-count cartons.

Comment: This is acceptable.

j. The statement "Keep the carton and package insert. They contain important information." appears on the top flap of the 14-count cartons and on the right side flap of the 28- and 42-count cartons.

Comment: This is approved RLD labeling and is acceptable.

k. The top flap of the 14-count cartons, the right side flap of the 28-count cartons, and the left side flap of the 42-count cartons contain the manufacturing information:

Manufactured by:
Dexcel Pharma Technologies Ltd.
10 Hakidma St. Yokneam 2069200, Israel

Comment: This complies with 21 CFR 201.1 and is acceptable.

ii. Outer Carton Drug Facts Label

See Section II.A.ii.a-e

Other Sections/Issues

The Drug Facts label does not comply with the specifications of 21CFR 201.66(d) in the following ways:

- For all bottle cartons, the ***Other Information*** and ***Inactive Ingredients*** sections of the Drug Facts label are not listed in the order required by 21 CFR 201.66(c)(7) and 201.66(c)(8).
- For the 14- and 28-count bottle cartons, the visual graphic arrows do not properly signal the continuation of the Drug Facts label to the next adjacent panel as required in 21 CFR 201.66(d)(5).
- For the 28-count bottles, the last section of the Drug Facts information appears in isolation and does not comply with 21 CFR 201.66(d)(7).

Comment: This is not acceptable. Revise the *Other Information* and *Inactive Ingredients* sections for all bottle cartons so that they are listed in the order required by 21 CFR 201.66(c)(7) and 201.66(c)(8). Revise the 14- and 28-count bottle cartons so that the visual graphic arrows properly signal the continuation of the Drug Facts label to the next adjacent panel as required in 21 CFR 201.66(d)(5), and revise the 28-count bottle cartons so that the last panel of the Drug Facts label complies with 21 CFR 201.66(d)(7).

iii. Immediate Container Labels:

a. **7-count blister**

The 7-count blister label was submitted on August 7, 2015, and was not discussed at the April 13, 2015 RTF meeting. (b) (4) [redacted] Conversely, it is possible that the use of pack sizes that are smaller than the recommended course of treatment could result in consumers taking less of the drug than is optimal for care. In order to address these issues, the sponsor should provide data to demonstrate that consumers understand labeled instructions that two packaged (b) (4) [redacted] blisters represent a full course of treatment.

Comment: This is not acceptable. A [redacted] (b) (4) is not approved labeling for the RLD or any other OTC PPI. Given the evidence that limiting pack sizes of medication may reduce consumption, it is possible that the use of pack sizes that are smaller than the recommended course of treatment could result in consumers taking less of the drug than is optimal for care. Consumers may determine the product is efficacious by day 7 and discontinue their treatment. [redacted] (b) (4) Provide data to demonstrate that consumers understand labeled instructions that two packaged [redacted] (b) (4) blisters represent a full course of treatment.

b. **14-count blister**
A 14-count blister immediate container is not approved labeling for the RLD, however the proposed 14-count blister label is identical to the approved blister label for other OTC products such as Prilosec OTC and Omeprazole. The blister label contains the identity statement, instructions to "Push tablet through foil" and the manufacturing information.

Comment: This is acceptable.

c. **14-count bottle**
- The statement "NOT FOR RESALE" appears on the top portion of the PDP of the bottle label.

  Comment: This is acceptable.

- The statement of identity appears below, with the prominence of the proprietary/established name diminished by the design and cluttered appearance of the PDP.

  Comment: This is not acceptable. See Section II.B.i.a for details.

- The declaration of net quantity of contents appears at the lower left corner of the PDP.

  Comment: This is acceptable.

- The statement "One 14-day course of treatment" appears underneath the declaration of net quantity.

  Comment: This is acceptable.

- The manufacturing information appears on the right side of the bottle label. See Section II.B.i.j for details.

  Comment: This is acceptable.

- The statements "Safety Feature – Do not use if printed seal under cap is broken or missing" and "(b) (4) appear on the left side of the bottle label.

  Comment: This is acceptable.

- On the back of the bottle label, the Drug Facts label information regarding the Active Ingredient, Purpose, Use and Other Information are provided. The remainder of the Drug Facts label is not required to appear on the bottle, as the bottle carton is seen by the consumer at the point of purchase.

  Comment: This is acceptable.

iv. Consumer Information Leaflet

The consumer information leaflet (CIL) is identical to the RLD except for the following:

a. The proprietary name Prevacid 24HR is replaced with the sponsor's established name "Lansoprazole delayed release orally disintegrating tablets" wherever it appears.

   Comment: This is acceptable.

b. Under the heading "**How to Take Lansoprazole delayed release orally disintegrating tablets 14-DAY Course of treatment**", the following bullets state:

   - **take 1 tablet before eating in the morning. Place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water**
   - **take every day for 14 days**
   - **do not take more than 1 tablet a day**
   - **do not crush or chew tablets**
   - **do not use for more than 14 days unless directed by your doctor.**
   - **do not take this medicine with alcohol**

   The RLD directions on how to take the drug are contained in the fourth bullet "[bullet] Swallow whole. Do not crush or chew tablets." The proposed labeling

moves the "Swallow whole" instruction to the first bullet and adds instructions on how to take the orally disintegrating tablet form. It also combines these statements with the instructions on the timing of the dose "Take 1 tablet before eating in the morning.", creating a long bullet that is conceptually very complex.

Comment: This is not acceptable. Create a separate bullet that only contains instructions on how to take the tablet, so that the section reads:

- **take 1 tablet before eating in the morning**
- **place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water.**
- **take every day for 14 days**
- **do not take more than 1 tablet a day**
- **Do not crush or chew tablets**
- **do not use for more than 14 days unless directed by your doctor**
- **do not take this medicine with alcohol**

c. (b) (4) **Keep out of reach of children.**
The Poison Control Center phone number has been added to the warning. See Section II.A.ii.b.

Comment: This is acceptable.

d. Under the heading "For Questions or Comments About Lansoprazole delayed release orally disintegrating tablets", the phone number is identified as 1-800-XXX-XXXX.

Comment: This is not acceptable. Replace the placeholder Xs with an actual telephone number. 21 CFR 201.66(c)(9) requires that this section contain a telephone number of a source to answer questions about the product. We also recommend that the label include the days of the week and times that the toll-free number is in operation.

e. The manufacturing information is added to the bottom of the CIL. See Section II.A.i.j. for details.

Comment: This is acceptable.

II. RECOMMENDATIONS

Please communicate the following to the sponsor:

A. The following revisions are to be made by the sponsor:

i. Non Drug Facts Labeling

a. For the proposed 7-count blister package, provide data to demonstrate that consumers understand labeled instructions that two packaged (b) (4) blisters represent a full course of treatment. (b) (4)

b. Increase the relative prominence of "Lansoprazole" on the cartons and bottle label consistent with the PDP design of the proposed labeling submitted on December 8, 2014, and discussed at the April 13, 2015 meeting between FDA and Dexcel. Because the established name will be the name marketed to the consumer, the other text on the submitted label competes for the consumer's attention on the PDP and may be confusing.

c. Submit 14-count bottle carton and 14-count bottle carton with window labels that display the name "Lansoprazole" on the PDP when printed.

d. Remove (b) (4) that is located adjacent to the tablet (b) (4) statement "May take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours". (b) (4)

e. For the blister carton labels, add the statement "Keep the carton and package insert. They contain important information" to the carton. This is approved labeling for the reference listed drug, and is included in the draft labeling for the bottle cartons.

f. For the 14-, 28- and 42-count bottle carton with window labels, remove the bulleted statements:
   - May take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours
   - Clinically Proved to Treat Frequent Heartburn

   The window design serves to shift the entire PDP to the bottom half of the carton. With half as much area, the additional text affects the prominence of required items such as the statement of identity and the declaration of net quantity of contents. 21 CFR 201.15(a)(4) and 201.15(a)(6) state that required statements can lack the required prominence by reason of "…use of label space for any word,

statement, design, or device which is not required by or under authority of the act to appear on the label;" and "…crowding with other written, printed or graphic matter". The two bulleted statements are not required labeling, and should be removed from the PDP of the bottle carton with window.

g. Revise the consumer information leaflet to reflect the related changes to the Drug Facts label.

ii. Drug Facts Label

a. Under the heading "14-Day Course of Treatment" in the ***Directions*** section, revise the bullets to state:

- take 1 tablet before eating in the morning
- place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water.
- take every day for 14 days
- do not take more than 1 tablet a day
- do not crush or chew tablets
- do not use for more than 14 days unless directed by your doctor
- do not take this medicine with alcohol

b. Revise the last bullet in the ***Directions*** section, to be identical to the approved statement in the reference listed drug:

- Children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition.

c. Revise the ***Questions?*** section to contain a telephone number.

d. For all blister carton labels, place a bar line between the warning, **Stop use and ask a doctor if** and the pregnancy/breastfeeding warning as required in 21 CFR 201.66(d)(5).

e. Revise the visual graphic arrows on the Drug Facts label of the 14-count inner and outer blister cartons to properly signal the continuation of the Drug Facts label, and properly format the ***Questions?*** section of the Drug Facts label to comply with 21 CFR 201.66(d)(5) and 201.66(d)(7).

f. For all bottle cartons, revise the ***Other Information*** and ***Inactive Ingredients*** sections so that they are listed in the order required by 21 CFR 201.66(c)(7) and 201.66(c)(8).

g. Revise all the 14- and 28-count bottle cartons so that the visual graphic arrows properly signal the continuation of the Drug Facts label to the next adjacent panel as required in 21 CFR 201.66(d)(5).

h. Revise both 28-count bottle cartons so that the last panel of the Drug Facts label complies with 21 CFR 201.66(d)(7).

B. We also recommend that the sponsor make the following revisions:

i. Drug Facts label:

a. ***Questions or comments*** section: include the time that the toll-free number is in operation.

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and were evaluated in this labeling review:

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

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

/s/

MARY R VIENNA
04/25/2016

RUTH E SCROGGS
04/25/2016

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:	April 22, 2016
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 208025
Product Name and Strength:	Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg
Product Type:	Single Ingredient Product
Rx or OTC:	OTC
Applicant/Sponsor Name:	Dexcel Pharma Technologies Ltd
Submission Date:	August 6, 2015
OSE RCM #:	2016-922
DMEPA Primary Reviewer:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed carton labeling for Lansoprazole delayed-release orally disintegrating tablets submitted to NDA 208025, for areas of vulnerability that could lead to medication errors.

The Applicant is seeking approval under a 505b2 application relying on the listed drug (LD) Prevacid 24HR (NDA 022327). Of note, the Applicant did not submit a proprietary name for this proposed product; however, they indicated that they plan to submit a request for proprietary name review once a distributor is identified (see DARRTS NDA 208025 Meeting Minutes, dated September 2, 2015).

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.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	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

The proposed carton labeling for Lansoprazole delayed-release orally disintegrating tablets contains the designation "(b) (4) The incorporation of an image of the product follows the same format as the currently marketed LD Prevacid 24HR capsules. However on the Prevacid 24HR PDP, the capsule image is located on the bottom left corner of the PDP and there is no (b) (4) On the PDP of the proposed Lansoprazole delayed-release orally disintegrating tablets, the (b) (4)

(b) (4)

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Figure 1. Proposed Lansoprazole delayed-release orally disintegrating tablets PDP (from the August 6, 2015 submission) and Prevacid 24HR PDP (from Drugs@FDA)

(b) (4)

4 CONCLUSION & RECOMMENDATIONS

We determined that the Lansoprazole delayed-release orally disintegrating tablets carton labeling could be improved to clarify and accurately portray important information in the carton labeling to promote safe use of the proposed product.

4.1 RECOMMENDATIONS FOR DEXCEL

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

A. Carton Labeling

1. Remove (b) (4)
2. Ensure that the image of the Lansoprazole delayed-release orally disintegrating tablet throughout all carton bottle sizes represents a true depiction of the actual tablet. The image should reflect the true tablet size, color, and imprint of the actual tablet.[1]

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

[1] Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.

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

/s/

GRACE JONES
04/22/2016

CHI-MING TU
04/22/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 208025	NDA Supplement #: N/A	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: To be determined/Proprietary Name Review Request not submitted by Sponsor Established/Proper Name: lansoprazole Dosage Form: delayed-release, orally-disintegrating tablet Strengths: 15 mg		
Applicant: Dexcel Pharma Technologies, Ltd. Agent for Applicant: Camargo Pharmaceutical Services, LLC		
Date of Application: 08/06/15 Date of Receipt: 08/07/15 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: 06/07/16	Action Goal Date (if different): N/A	
Filing Date: 10/06/15	Date of Filing Meeting: 09/15/15	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☒ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of frequent heartburn (occurring 2 or more days a week) in adults age 18 years and older.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: N/A ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☒
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☒ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): DGIEP	
List referenced IND Number(s): Sponsor referenced no INDs. (See PIND 118528)	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		N/A
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☒	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients*	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

(including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Full waiver granted
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☒	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☒ **Not applicable**			
Check all types of labeling submitted.	☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☐	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☐	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☐	☐	☐	
Has a review of the available pregnancy and lactation data been included?	☐	☐	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☐	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☐	☐	☐	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☒ Outer carton label ☒ Immediate container label ☒ Blister card ☒ Blister backing label ☒ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

[5] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☒	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☒	
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 09/15/15

BACKGROUND: The NDA 208025 Resubmission/After Refuse to File was submitted on 08/06/15 and received on 08/07/15. The Refusal to File letter was issued 02/06/15. A Type A meeting was held 04/13/15.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jeffrey Buchanan	N
	CPMS/TL:	Dan Brum	Y
Cross-Discipline Team Leader (CDTL)	Francis Becker		Y
Division Director/Deputy	Karen Mahoney		Y
Office Director/Deputy	Theresa Michele		N
Clinical	Reviewer:	Ketan Parikh	Y
	TL:	Francis Becker	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	Mary Vienna	Y
	TL:	Steve Adah Betsy Scroggs	N Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Sandhya Apparaju	Y
	TL:	Sue Chih Lee	
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:		

	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wafa Harrouk	Y
	TL:	Paul Brown	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Swapan De	Y
	RBPM:	Thao Vu	
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:	Muthukumar Ramaswamy	
• Process	Reviewer:	Pei-I Chu Ubrani Venkataram	Y Y
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:	Mei Ou	
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	Danae Christodoulou		N
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Grace Jones	Y
	TL:	Chi-Ming Tu Jenna Lyndly	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• DGIEP *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:	Kerry Jo Lee	
	TL:	Jessica J. Lee	
Other attendees	Sherry Stewart, RPM, DNDP		Y
	Erin Skoda, Div of Life Cycle API		
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO BA/BE studies
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: BA/BE studies	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES – see 10/08/15 request ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: Biopharm review issues identified	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Karen Murry Mahoney, MD, Deputy Director, DNDP **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

JEFFREY A BUCHANAN
10/09/2015

Filing Review for Lansoprazole

SUBMISSION DATES:	December 8, 2014 and August 6, 2015
NDA/SUBMISSION TYPE:	NDA 208025
ACTIVE INGREDIENTS:	Lansoprazole, 15 mg
DOSAGE FORMS:	Delayed release orally disintegrating tablets
SPONSOR:	Dexcel Pharma Technologies, Ltd. Camargo Pharmaceutical Services, LLC: U.S. Agent Ruth E. Stevens, Ph.D., M.B.A. Chief Scientific Officer, Executive Vice President
REVIEWER:	Mary R. Vienna, R.N., M.H.A.
TEAM LEADER:	Steven Adah, Ph.D.

Submitted Labeling	Representative of Following SKUs
7-count immediate container (blister)	N/A
14-count immediate container (blister)	N/A
14-count immediate container (bottle)	N/A
14-count inner carton (blister)	N/A
14-count carton (blister)	N/A
14-count carton (bottle)	N/A
14-count carton with window (bottle)	N/A
28-count carton (blister)	N/A
28-count carton (bottle)	N/A
28-count carton with window (bottle)	N/A
42-count carton (blister)	N/A
42-count carton (bottle)	N/A
42-count carton with window (bottle)	N/A

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	N/A	This is a new NDA
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	Yes	
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	N/A	
Is distributor labeling included?	No	
Does the submission include the annotated specifications for the Drug Facts label?	Yes	
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	Yes	
Do any of the labels include "prescription strength" or similar statements?	No	
Do any of the labels include "#1 doctor recommended" or similar endorsement statements?	No	
Do any labels include text in a language other than English?	No	
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	No	No trade name proposed
Does a medical officer need to review any clinical issues?	Yes	New NDA
If SLR, should ONDQA also review?	N/A	

Information Request:
No information request is necessary.

Reviewer's Comment:

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

/s/

MARY R VIENNA
09/21/2015

RUTH E SCROGGS
09/21/2015
signing for Steve Adah, TL

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

<table>
<tr><th colspan="4">Application Information</th></tr>
<tr><td>NDA # 208025</td><td colspan="2">NDA Supplement #: S- N/A</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Animal Rule Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Pediatric</td></tr>
<tr><td colspan="4">Proprietary Name: To be determined/Proprietary Name Review Request not submitted by Sponsor
Established/Proper Name: lansoprazole
Dosage Form: delayed-release, orally-disintegrating tablet
Strengths: 15 mg</td></tr>
<tr><td colspan="4">Applicant: Dexcel Pharma Technologies, Ltd.
Agent for Applicant (if applicable): Camargo Pharmaceutical Services, LLC</td></tr>
<tr><td colspan="4">Date of Application: 12/05/14
Date of Receipt: 12/08/14
Date clock started after UN: N/A</td></tr>
<tr><td colspan="2">PDUFA Goal Date: 10/08/15</td><td colspan="2">Action Goal Date (if different): N/A</td></tr>
<tr><td colspan="2">Filing Date: 02/06/15</td><td colspan="2">Date of Filing Meeting: 01/29/15</td></tr>
<tr><td colspan="4">Chemical Classification (original NDAs only) :
☐ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☒ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch</td></tr>
<tr><td colspan="4">Proposed indication(s)/Proposed change(s): Treatment of frequent heartburn in adults age 18 years and older.</td></tr>
<tr><td colspan="3">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement: N/A

If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>☐ 505(b)(1)
☒ 505(b)(2)
☐ 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): DGIEP	
List referenced IND Number(s): Sponsor referenced no INDs. (See PIND 118528)	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☒	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☐	☒		See RTF Letter dated 02/06/15

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain. Some navigable hyperlinks were missing				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	Submitted as amendment, 02/04/15
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	Full waiver granted
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☒	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☒ **Not applicable**			
Check all types of labeling submitted.	☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☐	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☐	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☐	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☐	☐	☐	
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☒ Outer carton label ☒ Immediate container label ☒ Blister card ☒ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☒	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☒	
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 29, 2015

BACKGROUND: NDA 208025 was submitted 12/05/14, received 12/08/14. An amendment to the application, in response to 01/30/15 and 02/02/15 Information Requests, was received on 02/04/15. The sponsor submitted several meeting requests under PIND 118528; however, the sponsor neither requested nor attended a pre-NDA meeting.
All requested disciplines were represented at the filing meeting.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jeffrey Buchanan	Y
	CPMS/TL:	Dan Brum	N
Cross-Discipline Team Leader (CDTL)	Jane Filie		Y
Division Director/Deputy	Theresa Michele Karen Mahoney		Y N
Office Director/Deputy	Charles Ganley Jagjit Grewal (ADRA)		N Y
Clinical	Reviewer:	Mona Khurana	Y
	TL:	Jane Filie	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	Mary Vienna	Y
	TL:	Steven Adah	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Sandhya Apparaju	Y
	TL:	Sue Chih Lee	N
Biostatistics	Reviewer:		

	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wafa Harrouk	Y
	TL:	Paul Brown	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Muthukumar Ramaswamy Swapan De	Y N
	TL:	Danae Christodoulou	Y
Biopharmaceutics	Reviewer	Tien Mien (Albert) Chen	Y
	TL:	Tapash Ghosh	N
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Grace Jones	Y
	TL:	Jenna Lyndly	Y
OSE/DRISK (REMS)	Reviewer:	Peter Diak	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:	Kerry Jo Lee (DGIEP)	Y
	TL:	Jessica J. Lee (DGIEP)	Y
Other attendees	Abiola Olagundoye (OSE) Catherine Tran-Zwanetz (ONDQA)		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues:	☐ Not Applicable
o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., BA/BE studies):	BA/BE Studies
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: See 02/06/15 RTF Letter	☐ Not Applicable ☐ No comments
CLINICAL **Comments**: See 02/06/15 RTF Letter	☐ Not Applicable ☐ FILE ☒ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: See 02/06/15 RTF Letter for ClinPharm Comments	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: See 02/06/15 RTF Letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: See 02/06/15 RTF Letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization? **Comments**:	☒ Not Applicable ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☒ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Theresa Michele, MD (Director, DNDP)

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☒	The application is unsuitable for filing. Explain why: See 02/06/15 RTF Letter
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☐	If priority review:

	• notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

JEFFREY A BUCHANAN
02/06/2015