

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209400Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 209400

SUPPL #

HFD # 560

Trade Name

Generic Name omeprazole delayed-release, orally disintegrating tablets

Applicant Name Dexcel Pharma Technologies

Approval Date, If Known 07/06/2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

Application is 505(b)(2).

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

- The sponsor has conducted a bioequivalence study and a bioavailability (food-effect) study to provide the scientific bridge to the agency's finding of safety and efficacy for Prilosec OTC (NDA 021229).

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021229	Prilosec OTC
NDA# 022056	Prilosec Delayed-release Suspension
NDA# 022032	Omeprazole delayed-release tablet

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only

if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

=====

Name of person completing form: Alina Salvatore
Title: Regulatory Project Manager
Date: 06/12/17

Name of Division Director signing form: Karen Murry Mahoney, MD, FACE
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
06/22/2017

KAREN M MAHONEY
07/05/2017

1.3 Administrative Information

1.3.3 Debarment Certification

Links are provided below to the debarment certifications included in this NDA.

Organization	Where Used
Dexcel Pharma Technologies Ltd.	Drug product manufacturer, Packaging and Quality testing (Dexcel Ltd.)
(b) (4)	

Dexcel Pharma Technologies Ltd

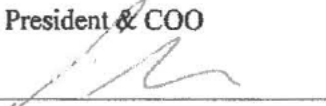
1 Dexcel Street Or Akiva 3065000, Israel • Tel: 972-4636-4080 • Fax: 972-153-4-6364080 • E-mail:

Certificate of Debarment

Dexcel Pharma Technologies Ltd. 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.

Name: Uri Oren

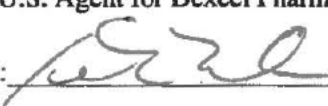
Title: Vice President & COO

Signature: 

Date: June 7, 2016

Name: Jeanne M. Novak, Ph.D.

Title: Authorized U.S. Agent for Dexcel Pharma Technologies Ltd.

Counter-signature: 

Date: September 6, 2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209400	NDA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Established/Proper Name: omeprazole delayed-release Dosage Form: orally disintegrating tablet		Applicant: Dexcel Pharma Technologies Ltd Agent for Applicant (if applicable): CBR International Corp
RPM: Alina Salvatore		Division: Nonprescription Drug Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>July 6, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 5 (new formulation or manufacturer)
(confirm chemical classification at time of approval)

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☒ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) Approval: 07/05/17
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☐ Included
Original applicant-proposed labeling	☐ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☐ Included
Original applicant-proposed labeling	☐ Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
Most-recent draft labeling	☒ Included
❖ Proprietary Name	N/A
- Acceptability/non-acceptability letter(s) (indicate date(s)) - Review(s) (indicate date(s))	
❖ Labeling reviews (indicate dates of reviews)	RPM: ☒ None DMEPA: ☒ None DMPP/PLT (DRISK): ☒ None OPDP: ☒ None SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None DNDP: 06/12/17, 05/23/17, 10/25/16 (Filing Review)
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review) ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing Review: completed in Oct 2016 and entered into DARRTS 06/02/17 ☐ Not a (b)(2) 06/05/17
❖ NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director)	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

Applicant is on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo <i>(indicate date)</i> - If yes, OC clearance for approval <i>(indicate date of clearance communication)</i>	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics <i>(approvals only)</i> Date reviewed by PeRC <u>06/07/17</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i>	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i> <i>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</i>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) <i>(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)</i>	Acknowledge NDA: 09/15/16 Filing Review Issues Identified: 11/19/16 Information Requests: 05/24/17, 04/26/17, 02/22/17
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	PeRC Meeting Minutes: 06/07/17
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☒ N/A or no mtg
Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	☐ No mtg 5/09/16
EOP2 meeting <i>(indicate date of mtg)</i>	☒ No mtg
Mid-cycle Communication <i>(indicate date of mtg)</i>	☒ N/A
Late-cycle Meeting <i>(indicate date of mtg)</i>	☒ N/A
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <i>(indicate dates of mtgs)</i>	Pre-IND Type B mtg: 10/06/15
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	☒ None
Division Director Summary Review <i>(indicate date for each review)</i>	☐ None 07/05/17
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	☐ None 06/13/17
PMR/PMC Development Templates <i>(indicate total number)</i>	☒ None

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	☒ No separate review
• Clinical review(s) (indicate date for each review)	05/04/17, 10/31/16 (filing review)
• Social scientist review(s) (if OTC drug) (indicate date for each review)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)	05/19/17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	☒ N/A
❖ Risk Management - REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) - REMS Memo(s) and letter(s) (indicate date(s)) - Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	N/A ☐ None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	☐ None requested 04/10/17
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☐ No separate review
Statistical Team Leader Review(s) (indicate date for each review)	☐ No separate review
Statistical Review(s) (indicate date for each review)	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)	☐ None 05/26/17, 10/26/16 (filing review)
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☒ None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ No separate review
• Supervisory Review(s) (indicate date for each review)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None 05/08/17, 11/02/16 (filing review)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (indicate date for each review)	☒ None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	☐ None 05/04/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	Completed in Integrated Quality Assessment 05/04/17
☐ Review & FONSI (indicate date of review)	N/A
☐ Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change))	☒ Acceptable 04/2017-OAI recommended: corrective action acceptable ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity <i>(Notify CDER OND IO)</i>
Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☐ Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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
07/06/2017

PeRC Meeting Minutes
June 7, 2017

PeRC Members Attending:

Lynne Yao
John Alexander
Skip Nelson
Meshaun Payne
Jacqueline Yancy
Hari Cheryl Sachs
Wiley Chambers
Susan McCune
Tom Smith
Victor Baum
Gil Burkhart
Donna Snyder
Kevin Krudys
Lily Mulugeta
Shrikant Pegay
Dionna Green
Rosemary Addy
James Travis
Mark Rothmann
Tim McGovern
Barbara Buchs
Julia Pinto

Agenda

Non-Responsive

10:20	NDA 209400	Omeprazole delayed-release, orally disintegrating tablet Full Waiver with Agreed iPSP	DNDP	Alina Salvatore	Treatment of frequent heartburn (occurring 2 or more days a week)
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	DNDI	P
Non-Responsive		

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

NON-RESPONSIVE

Omeprazole delayed-release, orally disintegrating tablet Full Waiver with Agreed iPSP

- Proposed Indication: Treatment of frequent heartburn (occurring 2 or more days of a week) in adults age 18 years and older
- This product triggers PREA as a new dosage form and has a PDUFA goal date of July 6, 2017.
- The sponsor states that the use of non-prescription OTC omeprazole delayed release ODT in all ages of the pediatric population would not be consistent with clinical practice recommendations since the underlying causes for heartburn in children should be evaluated by a healthcare professional.

- The sponsor plans to request full waiver of the pediatric population as the product would be ineffective and/or unsafe in one or more of the pediatric group for which a waiver is being requested.
- Heartburn is not a condition that can be diagnosed without a learned intermediary.
- The division states that the drug facts label will say for adults 18 years of age and older. Children under 18 years of age see your doctor. Heartburn in children may be a serious condition.
- PeRC Recommendations:
 - o The PeRC agrees to full waiver for of the pediatric population.

NON-RESPONSIVE

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/s/

JACQUILINE A YANCY
06/23/2017

From: Salvatore, Alina
To: ["Monica Rohrschneider"](#)
Cc: [Jeanne Novak](#); [Mara Holinger](#)
Subject: Information Request for NDA 209400-Due June 2, 2017
Date: Wednesday, May 24, 2017 9:01:00 AM
Attachments: [NDA 209400 Labeling Comments.docx](#)

Dear Monica,

Please confirm receipt of this email and see the attached Information Request for NDA 209400.

Please provide a response by COB June 2nd.

Thank you,

Alina

Alina W. Salvatore, RPh, MS, RAC
CAPT, United States Public Health Service
Senior Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 240-402-0379

The information transmitted in this electronic communication is intended only for the person or entity to whom it is addressed and may contain confidential and/or privileged material. Any review, retransmission, dissemination or other use of or taking of any action in reliance upon this information by persons or entities other than the intended recipient is prohibited.

NDA 209400 Labeling Comments

The following revisions are to be made by the sponsor:

Non Drug Facts Labeling

1. Revise the graphic image of the orally disintegrating tablet so that it is not distorted and reflects the “Actual size” statement on the carton. We recommend revising the image to be similar to the orally disintegrating tablet graphic approved for your NDA 208025, S-003.
2. For the 2-count immediate container (blister), revise the statement (b) (4) at the top of the foil label to read “First two doses of a 14-day course of treatment” to reflect the correct dose

Drug Facts Label

3. **Ask a doctor or pharmacist before use if you are taking:** section, unbold the word “taking” in the warning title to comply with 21CFR 201.66(c)(5)(v) and the approved DFL of the listed drug.
4. **Stop use and ask a doctor if:** section, add a fifth bullet “[bullet] you develop rash or joint pain” after the bullet that reads “you get diarrhea” to conform to the change requested in the April 6, 2017 CBE-0 supplement request letter that was issued for the listed drug, NDA 021229.
5. **Keep out of reach of children** section, add a period at the end of the second sentence as approved in the DFL of the listed drug.
6. **Directions** “14-Day Course of Treatment” and “Repeated 14-Day Courses (if needed)” sections, revise the format of this section to indent both headings and the bullets under each heading to make them subordinate to the previous three bullets under the *Directions* section. Ensure that the “children under 18 years of age: ask a doctor before use” bullet is formatted so that it is not aligned with the “14-Day Course of Treatment” and “Repeated 14-Day Courses (if needed)” sections, but is moved out to align with the first three bullets under the Directions section. Refer to the approved DFL for the listed drug, NDA 021229, S-026.
7. **Directions** “14-Day Course of Treatment” section, add a period after the second sentence of the third bullet so that the statement reads “[bullet] place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water.” Refer to the approved DFL for NDA 208025.
8. **Other Information** Revise the third bullet to read “[bullet] store at 20-25°C (68-77°F); keep product out of high heat and moisture”

We also recommend that the sponsor make the following revision:

Drug Facts label. **Questions or comments?:** include the time that the toll-free number is operating.

Recommend that the sponsor print out draft labels and check for accuracy before submitting to ensure resolution of the technical issues with missing information on printed labels.

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/s/

ALINA W SALVATORE
05/24/2017

Clinical Investigator Financial Disclosure
Review

Application Number: 209400

Submission Date(s): September 6, 2016

Applicant: Dexcel Pharma Technologies Ltd.

Product: Omeprazole delayed release orally disintegrating tablet 20 mg

Reviewer: Ryan Raffaelli, M.D.

Date of Review: May 19, 2017

Covered Clinical Study (Name and/or Number): Protocol 150075

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>10</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>None</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>None</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Clinical Investigator Financial Disclosure
Review

Application Number: 209400

Submission Date(s): September 6, 2016

Applicant: Dexcel Pharma Technologies Ltd.

Product: Omeprazole delayed release orally disintegrating tablet 20 mg

Reviewer: Ryan Raffaelli, M.D.

Date of Review: May 19, 2017

Covered Clinical Study (Name and/or Number): Protocol 150076

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>9</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>None</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>None</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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/s/

RYAN M RAFFAELLI
05/19/2017

From: Salvatore, Alina
To: [Monica Rohrschneider \(mrohrschnaider@cbrintl.com\)](mailto:mrohrschnaider@cbrintl.com)
Cc: [Mara Holinger](mailto:Mara.Holinger); [Jeanne Novak \(jnovak@cbrintl.com\)](mailto:jnovak@cbrintl.com)
Subject: Information Request for NDA 209400
Date: Wednesday, April 26, 2017 11:19:00 AM
Importance: High

Dear Monica,

Below is an information request related to the above referenced NDA. Please respond by COB Friday, May 5, 2017.

1. Submit samples of the tablet and an outer carton to verify tablet appearance and the "Actual size" claim on the PDP.
2. Resubmit the 14-count and 28-count bottle carton labels, as the net quantity statement does not appear on the label when printed.

Thank you,
Alina

Alina W. Salvatore, RPh, MS, RAC
CAPT, United States Public Health Service
Senior Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 240-402-0379

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/s/

ALINA W SALVATORE
04/26/2017



NDA 209400

**INFORMATION REQUEST
PATENT CERTIFICATION OR VERIFICATION**

Dexcel Pharma Technologies Ltd.
Attention: Jeanne Novak, PhD (US Agent, CBR International Corp)
CEO and Principal Consultant
2905 Wilderness Place, Suite 202
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated and received September 6, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for omeprazole delayed-release, orally disintegrating tablets, 20 mg.

We also refer to your amendments dated December 16, 2016 and January 6, 2017. These amendments do not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a "recertification" for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

- To add a new indication or other condition of use;
- To add a new strength;
- To make other than minor changes in product formulation; or
- To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

We recommend that the cover letter for your response to this information request and for future amendments to your unapproved 505(b)(2) application either:

- 1) states that the amendments contain a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or

- 2) verifies that the proposed change described in each amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

Your response to this information request must clearly reference your amendments dated December 16, 2016 and January 6, 2017.

If you have any questions, contact me at (240) 402-0379.

Sincerely,

{See appended electronic signature page}

Alina Salvatore, RPh, MS, RAC
Senior Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

ALINA W SALVATORE
02/22/2017



NDA 209400

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Dexcel Pharma Technologies Ltd.
Attention: Jeanne Novak, PhD (US Agent, CBR International Corp)
CEO and Principal Consultant
2905 Wilderness Place, Suite 202
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your New Drug Application (NDA) dated and received September 6, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for omeprazole delayed-release, orally disintegrating tablets, 20 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 6, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 9, 2017.

During our filing review of your application, we identified the following potential review issues. We request that you submit the following information by December 16, 2016.

A. Clinical

1. Provide, or identify the location of, a justification for determining that data from foreign studies, intended to support this application, are applicable to the U.S. population for which the drug is intended.

B. Chemistry, Manufacturing and Controls (Biopharmaceutics)

1. The following specification at acid stage was identified for your proposed product:

- N.L.T. (b)(4)% in 120 minutes

This wording is easily confused as “Not less than (b)(4)% of the dissolved omeprazole label claim in 120 minutes”. We follow the USP and recommend revising the wording to “No more than (NMT) (b)(4)% release in 120 minutes (in Acid Stage)”

2. The proposed dissolution specification for buffer stage is not consistent throughout the submission. The specification “NLT (b)(4)% (Q) in 30 minutes” was proposed in the following documents:

- 3.2.P.5.1 Specifications
- 3.2.P.5.6 Justification of Specifications
- 3.2.P.2 Pharmaceuticals development

However, a different specification “NLT (b)(4)% (Q) in 30 minutes (or (b)(4)) (b)(4)” was cited in other documents:

- 3.2.P.5.3 Val Analyte Proc Dissolution OMEP406R
- 3.2.P.5.4 Batch analyses

Clarify the discrepancy and correct as necessary.

3. You provided the mean disintegration data for each batch instead of the individual data. Submit the complete disintegration data (individual, mean, SD, RSD) for both release and stability tests.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUEST FOR PROPRIETARY NAME REVIEW

If you intend to have a proprietary name for the proposed product, please submit a new, complete, request for proprietary name review. Include the statement "**REQUEST FOR**

PROPRIETARY NAME REVIEW,” in bold capital letters, at the top of your cover letter and on the first page of the main submission document. The review of this name will be initiated when the new submission is received.

If you require additional information on developing proprietary names for drugs or proposing alternative proprietary names for consideration, we refer you to the following documents:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We reference the waiver granted on March 4, 2016, for the pediatric study requirement for this application.

If you have any questions, call Alina Salvatore, Regulatory Project Manager, at (240) 402-0379.

Sincerely,

{See appended electronic signature page}

Karen Murry Mahoney, MD, FACE
Deputy Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

KAREN M MAHONEY
11/19/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209400
Dexcel Pharma Technologies Ltd.
Attention: Jeanne Novak, PhD (US Agent, CBR International Corp)
CEO and Principal Consultant
2905 Wilderness Place, Suite 202
Boulder, CO 80301

Dear Dr. Novak:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Omeprazole delayed-release orally disintegrating tablet, 20 mg

Date of Application: September 6, 2016

Date of Receipt: September 6, 2016

Our Reference Number: NDA 209400

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 5, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Nonprescription Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-0379.

Sincerely,

{See appended electronic signature page}

Alina Salvatore, RPh, MS, RAC
Senior Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

ALINA W SALVATORE
09/15/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 127169

MEETING MINUTES

Dexcel Pharma Technologies, Ltd.
Attention: Mara Holinger, PhD (US Agent)
Director of Regulatory Affairs, CBR International Corp.
2905 Wilderness Place, Suite 202
Boulder, CO 80301

Dear Dr. Holinger:

Please refer to your Pre-Investigational New Drug Application (PIND) file for omeprazole delayed-release orally disintegrating tablet, 20 mg.

We also refer to the meeting between representatives of your firm and the FDA on May 9, 2016. The purpose of the meeting was to discuss the format and content of your forthcoming NDA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alina Salvatore, Regulatory Project Manager at (240) 402-0379.

Sincerely,

{See appended electronic signature page}

Karen Murry Mahoney, MD, FACE
Deputy Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: May 9, 2016 at 9 AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: PIND 127169
Product Name: Omeprazole delayed-release orally disintegrating tablet, 20 mg
Indication: Treatment of frequent heartburn occurring 2 or more days a week
Sponsor/Applicant Name: Dexcel Pharma Technologies, Ltd.

Meeting Chair: Karen Murry Mahoney, MD, FACE
Meeting Recorder: Alina Salvatore, RPh, MS, RAC

FDA ATTENDEES

Office of New Drugs, Immediate Office

Jagjit Grewal, MPH, Associate Director for Regulatory Affairs

Division of Nonprescription Drug Products

Karen Murry Mahoney, MD, Deputy Director

Frank Becker, MD, Clinical Team Leader

Ryan Raffaelli, MD, Clinical Reviewer

Jane Sohn, PhD, Pharmacology/Toxicology Team Leader

Charlie Donald Thompson, PhD, Pharmacology/Toxicology Reviewer

Betsy Scroggs, PharmD, Associate Director of Labeling

Steven Adah, PhD, Interdisciplinary Scientist Team Leader

Mary Vienna, MHA, Interdisciplinary Scientist

Dan Brum, PharmD, MBA, BCPS, RAC, Chief, Project Management Staff

Alina Salvatore, RPh, MS, RAC, Regulatory Project Manager

Lori Griner, ORISE Fellow

Office of Pharmaceutical Quality/Office of New Drug Products

Swapan De, PhD, CMC Lead

Office of Clinical Pharmacology

Sue Chih Lee, PhD, Clinical Pharmacology Team Leader
Dilara Jappar, PhD, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality/Division of Biopharmaceutics

Tien-Mien Chen, PhD, Biopharmaceutical Quality Assessment Team Lead
Peng Duan, PhD, Biopharmaceutical Quality Assessment Reviewer

SPONSOR ATTENDEES

Dexcel Pharma Technologies, Ltd.

Tomer Gold, Vice President, Research and Development
Keren Agmon, Head of R&D Regulatory Affairs
Sigalit Melcer, Manager, Clinical Trials Department

(b) (4)

Via teleconference

Ilan Miller, Intellectual Property and Medical Information Manager
Valerie Azoulay, Pharmaceutical R&D Manager
Liora Gerad, Project Manager, Regulatory Affairs

(b) (4)

1.0 BACKGROUND

On March 21, 2016, Dexcel Pharma Technologies (DPT) submitted a meeting request to discuss the data and information, for omeprazole delayed-release (DR) orally disintegrating tablet (ODT), that will be included in a planned NDA submission, and specific topics related to the clinical investigation conducted in support of the NDA.

DPT intends to submit a 505(b)(2) New Drug Application (NDA) in June 2016. The sponsor intends to rely on FDA's findings of safety and efficacy of Prilosec OTC (NDA 021229), and cross-reference information in the sponsor's marketing application for omeprazole delayed-release tablets, 20 mg (NDA 022032). A pre-IND meeting was held on October 6, 2015, and meeting minutes were issued by FDA on November 3, 2015.

The sponsor's questions are **bolded**; FDA's preliminary responses are *italicized* and discussion is in normal font.

2.0 DISCUSSION

Regulatory

Question 1:

Does the Agency agree that the reference to DPT's marketing application for Omeprazole DR (NDA 022032), and reliance on FDA's findings of safety and effectiveness for Prilosec OTC (NDA 021229) are sufficient to support the 505(b)(2) application?

FDA Preliminary Comment:

In general, your proposal to cross-reference NDA 022032 omeprazole DR tablet and rely on FDA's findings of safety and effectiveness for NDA 021229 Prilosec OTC appears acceptable.

Also, your proposal to rely upon literature to support the safety of ascorbic acid in your product is acceptable (see Question 15 below). Note that page 42 of your briefing package states that ascorbic acid is listed as a GRAS substance that can be added to foods (21 CFR §182.3013) and is a common component of edible foods. Be advised that a 505(b)(2) applicant may not rely upon a finding that a substance is GRAS for one or more food uses for a determination of nonclinical safety for the use of that substance in a drug product. Such a GRAS designation is neither FDA's finding of safety and/or effectiveness for a listed drug, nor is it published literature. However, an applicant may obtain a right of reference to the studies that supported the GRAS finding or rely on the study findings if they have been published in scientific literature.

As an additional comment, we note that your NDA 022032 relied upon FDA's findings of safety and effectiveness for NDA 021229 Prilosec OTC and NDA 019810 Prilosec DR capsules. If the cross-referenced portions of your previously approved 505(b)(2) application (NDA 022032) involve reliance on FDA's finding of safety and/or effectiveness for NDA 019810 Prilosec DR capsules, then your new 505(b)(2) application should also identify NDA 019810 as a listed drug being relied upon in accordance with FDA's regulations at 21 CFR 314.54. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification/statement and notification), apply to each listed drug upon which an applicant relies.

Discussion:

DPT will provide pharmacokinetic (PK) data comparing its omeprazole DR ODT to its omeprazole DR tablet. DPT is not planning to submit dissolution data comparing its proposed omeprazole DR ODT to Prilosec OTC for bioequivalence (BE) determination purposes. The sponsor confirmed that it intends to cite reliance on the listed drug product, Prilosec OTC. DPT intends to only cross-reference its NDA 022032 with respect to the BE study comparing its omeprazole DR tablet to Prilosec OTC which established a bridge to rely on FDA's findings of safety and effectiveness for Prilosec OTC. The sponsor clarified that it does not intend to rely on FDA's findings of safety and efficacy for NDA 019810 Prilosec DR capsules. FDA found this plan to be generally acceptable noting that the preliminary comments with regard to NDA 019810 are recommended to be taken under advisement as the sponsor develops the planned 505(b)(2) NDA.

Postmeeting Comment:

Include in the NDA the dissolution information and data for the biobatches used in the PK study, primarily to ensure quality control.

Question 2:

Does the Agency agree that a waiver for pediatric studies in children under the age of 18 is acceptable for DPT's new Omeprazole ODT product?

FDA Preliminary Comment:

Refer to the Agreed iPSP correspondence dated March 4, 2016. At this time, we agree that a waiver for pediatric studies is appropriate. Include a copy of the Agreed iPSP document in your planned NDA.

CMC

Question 3:

Does the Agency agree that the new specifications of the API approved in S-031 of NDA 022032 can be adopted for the current proposed 505(b)(2) NDA?

FDA Preliminary Comment:

Yes, we agree. Provide your acceptance criteria for the drug substance in the NDA with supporting batch analysis data.

Question 4:

The Sponsor intends to propose

(b) (4)

The change in scale will involve a change in equipment volume and optimization of process parameters, and will be validated. No changes in the process will be made and no changes in the class of the equipment will be made. The manufacturing process, list of equipment and the control strategy for both batch sizes is provided in [Attachment 2](#).

Does the Agency agree that the Sponsor can report the intended scale up in a CBE?

FDA Preliminary Comment:

In your NDA application, provide a comparability protocol for your scale-up changes. The comparability protocol will be reviewed as part of your NDA submission and you will be advised regarding the reporting category of your future supplement.

Discussion:

FDA confirmed that a comparability protocol, submitted for review in the NDA, is preferred over submitting a supplement postapproval.

Question 5:

The specifications of the proposed product are provided in Table 5, and include (b) (4) as a known impurity. The justification for the inclusion of (b) (4) is provided in the CMC section.

- Does the Agency agree with the proposed specification for the drug product?
- Does the Agency agree with the proposed specification for (b) (4)?

FDA Preliminary Comment:

With regard to your specifications on disintegration time and dissolution, no, we do not agree:

- 1. In order to claim that your product is an ODT, as described in the guidance for industry Orally Disintegrating Tablets, the in vitro disintegration time should be approximately 30 seconds or less.*
- 2. Delayed release (enteric coated) products should have specifications established in both acid stage and buffer stage per U.S. Pharmacopeia (USP).*
 - Acid Stage: No individual tablet exceeds 10% dissolved at 2 hours.*
 - Buffer Stage-IR: For immediate release (IR), the selection of the specification time point X should be where Q=80% dissolution/release occurs.*
 - Buffer Stage-ER: For extended release (ER), set the establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data. Base the specification ranges on the overall dissolution data generated at these times. In general, the selection of the dissolution specification ranges is based on mean target value $\pm 10\%$ and NLT 80% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved/established In Vitro-In Vivo Correlation (IVIVC) model.*

Note that the final determination on the acceptability of the proposed acceptance criteria for your product will be made during the NDA review based on the provided data.

We agree with your proposal to include (b) (4) as a specification in the drug product; however, the acceptance limit for this impurity will be evaluated during NDA review, based on available release and stability data. Refer to ICH Q3B(R) for setting limits for drug product impurities and degradants.

Discussion:

In order to obtain the ODT claim, as described in the guidance for industry *Orally Disintegrating Tablets*, the in vitro disintegration time should be approximately 30 seconds or less. The final determination on the acceptability of the proposed specifications for in vitro disintegration time will be made during review of the NDA and will be based on the totality of the data provided (i.e., in vitro disintegration time at time zero upon manufacture and also during the stability program supporting the shelf life claim), the sponsor's justifications, and knowledge of approved ODT drug products.

In regard to the acid stage comment, DPT requested feedback on use of a gastric resistance test versus the acid test.

Postmeeting Comment:

Two-stage testing could be conducted and two sets of the delayed-release ODT tablets (n=12/set) employed simultaneously as follows:

1. After remaining in Acid Stage for 2 hours, one set of tablets of the proposed drug product is processed for analysis after breaking down its enteric coating to release the remaining amount of the labeled drug and the remaining amount could be measured to determine the specification at Acid Stage. The guidance states that “No individual tablet exceeds 10% dissolved at 2 hours.”
2. After remaining in the Acid Stage for 2 hours, the second set of tablets could be tested further at Buffer Stage to obtain the dissolution profile at Buffer Stage. For a drug product with proposed immediate release characteristics at Buffer Stage, the selection of the specification at time point X should be where $Q = \frac{(b) (4)}{(4)}\%$ dissolution/release occurs.

The final determination on the acceptability of the proposed specifications for in vitro disintegration time will be made during the NDA review process based on the provided data.

Question 6:

The Sponsor intends to provide results for (b) (4) in order to show that the drug product has a (b) (4) and it is not capable of supporting microbial proliferation. Does the agency agree that routine microbiological testing is unnecessary if the result for (b) (4) is less than (b) (4) %?

FDA Preliminary Comment:

This will be a review issue. When you submit the NDA, include your rationale and microbial testing for your NDA batches to support your proposal for not performing microbial testing.

Clinical Pharmacology

Question 7:

In order to support the approval of the proposed NDA, and to provide a scientific bridge to Prilosec OTC, the Sponsor intends to rely on PK study (AA24171, Omeprazole DR vs. Prilosec OTC) submitted in NDA 022032 and on PK study 150075 (Omeprazole ODT vs. Omeprazole DR) conducted for the proposed 505 (b)(2) NDA. Based on the PK ratios obtained in both studies (see [Table 7](#)), the Sponsor believes that the scientific bridge between Omeprazole ODT and both Omeprazole DR and Prilosec OTC is established, and that there is no risk for a bio-creep between Prilosec OTC and Omeprazole ODT.

Does the Agency agree that, based on the demonstration of bioequivalence with Omeprazole DR, the Sponsor can rely on FDA’s findings of safety and efficacy of Prilosec OTC (NDA 021229) and the data and information in Omeprazole DR (NDA 022032) for purposes of supporting the approval of the proposed Omeprazole DR ODT drug product?

FDA Preliminary Comment:

Your approach appears to be reasonable based on the preliminary results provided in the meeting package. See also preliminary comments to Question 1.

Question 8:

Does the Agency agree that the bioequivalence study using Omeprazole DR as a reference drug, along with the bioavailability (food effect) study are sufficient for gaining an approval of the 505 (b)(2) NDA?

FDA Preliminary Comment:

Your approach appears to be reasonable based on the preliminary results provided in the meeting package. Whether the data are sufficient for gaining approval is a matter for the review of an NDA.

Question 9:

The proposed Omeprazole ODT drug product was determined to be bioequivalent to Omeprazole DR (NDA 022032), regardless of dosing condition (with or without water). Does the Agency agree with the proposed direction: "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."?

FDA Preliminary Comment:

Based on the preliminary results provided in the meeting package, the proposed directions appear to be reasonable. Final determination will occur following complete review of the NDA.

Question 10:

The Sponsor has conducted a dose dumping study, which revealed that the product is stable in alcohol concentration of 0%-20% but not in 40%. Therefore, the proposed labeling ([Attachment 3](#)) will include under the direction section "do not take this medicine with alcohol".

Does the Agency agree with the proposed direction with respect to the use of alcohol?

FDA Preliminary Comment:

Based on preliminary data, this appears reasonable. A final determination will be made after review of the NDA.

Discussion:

The sponsor stated that it does not plan to do in vivo testing.

Clinical

Question 11:

Does the Agency agree that, based on the similar PK ratios, and based on FDA's determination of safety and efficacy for Prilosec OTC, no additional clinical studies are required to support the safety and efficacy of the proposed product?

FDA Preliminary Comment:

We agree that no additional clinical trials appear to be required to support safety and efficacy.

Question 12:

The Sponsor plans to submit an Integrated Summary of Safety which will include the following data:

- **A summary of the AEs of the BE/BA studies, and results of oropharyngeal assessment.**
- **A summary of safety data of the two clinical studies conducted for the approval of Prilosec OTC.**
- **A summary of AEs reported in the literature related to the use of Omeprazole from January 2011-February 2016.**
- **A summary of safety information from Post-marketing databases: 1) FDA Adverse Event Reporting System (FAERS) database covering the period of January 2012-2015Q2. 2) Safety information from the American Association of Poison Control Centers (NPDS) covering the period of 2012-2015. 3) A summary of the data from the Drug Abuse Warning Network (DAWN) during 2011. A summary of WHO publications (Newsletters, WHO Drug information, Drug alert) covering the period of 2011-2016.**
- **A summary of Post marketing safety data for DPT's product Omeprazole DR from 2012-2015.**

Does the Agency agree that the proposed sources as well as the proposed targeted time windows are sufficient to support the safety portion of the NDA?

FDA Preliminary Comment:

We agree with your proposals overall and we have the following additional comments:

- *In your NDA, describe the pooling strategy for your safety analysis.*
- *Include the details on how the oropharyngeal assessments were conducted and any scales used to perform them.*
- *For the postmarketing database reviews, begin with the time of initial marketing of your omeprazole DR 20 mg product (NDA 22032.)*
 - *In Table 11 (Attachment 4, p. 66 of your background material) include events reported for pediatric users (< 18 years of age).*
 - *In Table 14 (Attachment 4, p. 68 of your background material), rather than only listing Preferred Terms reported by total number ($N \geq 20$), also report the Terms as percentages of the total events received, e.g., $\geq 1\%$, or $\geq 2\%$ if the length of the table would be unreasonably large.*
 - *Within the SOC's, sort Preferred Terms by decreasing order of frequency*
 - *Address the following safety topics of interest based on your review of the postmarketing databases and use (or misuse, i.e., Rx-only doses, duration > 14 days, or > 3 courses in one year) of omeprazole in the OTC setting: fractures and osteoporosis, Clostridium difficile diarrhea, hypomagnesemia (e.g., associated cardiac arrhythmias, palpitations, muscle spasms, convulsions).*
 - *Provide a 4-month safety update at the appropriate time after submission of your NDA.*

- *Provide synthesized conclusions about the published literature relevant to safe OTC use of omeprazole. Provide a table summarizing the literature with design of trials, objectives, subject enrollment eligibility relevant to the target OTC population, dosing regimen(s), and adverse events reported, with focus on the known safety signals associated with use of proton pump inhibitors. Provide copies of all articles retrieved. Five years of review are acceptable, with a maximum of six months between the search criterion last-publication date and the date of NDA submission.*
- *For omeprazole delayed release ODT marketed as a nonprescription product in any countries outside the U.S., provide a list of countries and certified English translations of those foreign labels. Also provide any information on whether nonprescription status has been withdrawn from any foreign markets for safety or regulatory reasons.*

Discussion:

In regard to bullet 3 above, FDA requested that the sponsor cover the same time period for review of all postmarketing databases. DPT commented that Tables 6 through 9 contain an NPDS data search through September 2015, and the sponsor will submit the 120-day safety update.

In regard to bullet 4 above, the sponsor will focus on the active ingredient omeprazole only.

Question 13:

The Sponsor included in [Attachment 4](#) the format of the tables that will be present in the ISS:

- **A table summarizing the AEs for each study with the following attributes: Subject, Age, Gender, Treatment arm/body system, adverse event description, MedDRA preferred Term, SOC, Severity, Related to study Drug, and Resolution.**
- **A table of the Incidence of Commonly Occurring AEs (>1 Subject of the Combined Overall Safety Population), stratified across System Organ Class MedDRA[®] Preferred Term.**
- **A table of all Adverse Dropouts Stratified by Treatment Arm with the Preferred Term of the Reported Adverse Event, with the following attributes: Study No., Subject, Age, Gender, Treatment, Dose, Body system, Adverse event, Preferred MedDRA term, Severity, and Outcome.**

Does the Agency agree that the proposed tables are acceptable to allow Agency review of the safety data?

FDA Preliminary Comment:

The proposed content and format of the proposed tables appears acceptable overall. We may ask for additional information, based on the findings, after we have begun review of your NDA.

Question 14:

The Sponsor conducted a single dose bioequivalence study and a food effect study. There were no clinically significant changes in any of the clinical laboratory tests. Though a tabulation of each laboratory test is generally part of the ISS format, the Sponsor does not

intend to specify the results for each test, and will only present a table which indicates that none of the subjects presented any significant changes in these parameters during the study (See [Table 14](#)).

Does the Agency agree that specific tables for each laboratory test, vital signs, and ECGs parameters are not required in the ISS?

FDA Preliminary Comment:

No, we do not agree. No summary tables are necessary, but provide tables with subject-level results and the original datasets of the tested parameters for our reference. Summarize the overall findings in the Integrated Summary of Safety.

Discussion:

The sponsor noted that during the previous PIND meeting, FDA agreed that full datasets would only be necessary if there were patterns of serious adverse events, deaths, or events associated with discontinuation. Since none were noted, FDA agreed that tables of individual data would suffice.

Non-Clinical:

No non clinical studies were conducted for the proposed product. The active substance

(b) (4)
(b) (4), and therefore is not expected to come into contact with the oral cavity. The safety of the excipients safety is supported by the FDA inactive ingredients database (IID): None of the excipients are novel. Given that the product is an ODT product, the level of the excipients used in the formulation was compared to the level in ODT dosage forms in the FDA IID. All the excipients which are suspected to be in contact with the oral cavity are below the maximum potency described for orally disintegrating tablets in FDA IID with the exception of ascorbic acid. Ascorbic acid is described in oral dosage form and suspension.

Question 15:

The Sponsor intends to submit a summary of safety based on literature reports for ascorbic acid, including a toxicological report, which supports the safety of the use of (b) (4) mg ascorbic acid in the proposed Omeprazole DR ODT. Based on the report, the Sponsor believes that the use of (b) (4) mg/tablet of ascorbic acid in the proposed ODT product does not pose a local or systemic safety concern. A summary of the report is included in the meeting package in [Section 10.5](#).

Does the Agency agree that no additional nonclinical studies are required to support the NDA of the proposed Omeprazole ODT product?

FDA Preliminary Comment:

You may rely on the FDA's previous findings of safety for the nonclinical portion of your NDA. The adequacy of any additional information provided with the NDA in support of the use of ascorbic acid as an excipient will be a matter of review.

The use of any novel excipient or excipient exceeding levels in currently approved oral products with similar use must be qualified for safety prior to approval as described in the guidance for industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients.

Provide structures of any impurities and degradants of the drug substance and drug product in your NDA submission. Monitor impurities and degradation products of all active ingredients and refer to ICH guidance [ICH Q3A(R2) and ICH Q3B(R)] for possible qualification requirements. Impurities or degradants of active ingredients that are identified as having mutagenic structural alerts must be at or below acceptable qualification thresholds to support an IND or NDA as described in the ICH M7 guidance, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. A final determination as to the adequacy of the data will be based on a full evaluation of all available information at the time of the NDA submission.

Labeling

Question 16:

DPT intends to include in the principal display panel of the label (b) (4)

(b) (4). The pictogram is not a part of the proprietary name (see Attachment 3-proposed labeling). The justification for the claim is that the product is an orally disintegrating tablet, therefore designed to disintegrate in the oral cavity, and then be swallowed.

Does the Agency agree that the proposed (b) (4) could be included in the labeling of the ODT product?

FDA Preliminary Comment:

(b) (4)

Discussion:

The sponsor commented that the (b) (4) identifies technology that differentiates the ODT product from their DR product. FDA acknowledged that descriptors are commonly used for this purpose, but the descriptors need to be clear and understood by consumers. The use of (b) (4) can imply a claim, and the meaning of the term (b) (4) may be unclear to consumers. Claims must be supported with data and labeling cannot be false or misleading. FDA noted that the sponsor could conduct a consumer study to demonstrate that the term (b) (4) is understood by consumers to mean an ODT. However, the Agency encouraged the sponsor to consider alternative descriptors for its ODT product. If the logo is not included on the principal

display panel at the time of NDA submission, FDA agreed that the sponsor may submit a prior approval labeling supplement, with the supporting data, after approval of the original NDA.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data

requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdeler-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the

CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by

reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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

/s/

KAREN M MAHONEY
06/09/2016



PIND 127169

MEETING MINUTES

Camargo Pharmaceutical Services, LLC
(U.S. Agent for Dexcel Pharma Technologies, Ltd.)
Attention: K. Gary Barnette, PhD
Vice President, Drug Development
2505 Meridian Parkway, Suite 175
Durham, NC 27713

Dear Dr. Barnette:

Please refer to your Pre-Investigational New Drug Application (PIND) file for omeprazole delayed-release, orally disintegrating tablets, 20 mg.

We also refer to the meeting between representatives of your firm and the FDA on October 6, 2015. The purpose of the meeting was to discuss your proposed nonprescription drug product development program.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have questions, contact Jeffrey Buchanan, Regulatory Health Project Manager, at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Karen Murry Mahoney, MD
Deputy Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-IND

Meeting Date and Time: Tuesday, October 6, 2015 at 2 p.m.
Meeting Location: FDA White Oak Campus
10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20993

Application Number: PIND 127169
Product Name: omeprazole delayed-release, orally disintegrating tablets, 20 mg
Indication: Treatment of frequent heartburn
Sponsor/Applicant Name: Dexcel Pharma Technologies, Ltd.

FDA ATTENDEES

Office of Drug Evaluation IV

Jagjit Grewal, MPH, Associate Director for Regulatory Affairs

Division of Nonprescription Drug Products

Karen Murry Mahoney, MD, Deputy Director
Francis Becker, MD, Medical Officer Team Leader
Ryan Raffaelli, MD, Medical Officer
Ruth E. Scroggs, PharmD, Associate Director for Labeling
Wafa Harrouk, PhD, Pharmacology/Toxicology Reviewer
Dan Brum, PharmD, MBA, BCPS, RAC, Chief, Project Management Staff
Jeffrey Buchanan, Regulatory Health Project Manager

Office of New Drug Products(ONDP)

Danae Christodoulou, PhD, Acting Branch Chief VI

ONDP/DB (Division of Biopharmaceutics)

Tien-Mien Chen, PhD, Biopharmaceutics Team Leader
Peng Duan, PhD, Biopharmaceutics Reviewer

Office of Clinical Pharmacology

Sue Chih Lee, PhD, Clinical Pharmacology Team Leader
Dilara Jappar, PhD, Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Dexcel Pharma Technologies, Ltd.

Tomer Gold, Vice President, Research and Development
Liora Gerad, PhD, Regulatory Affairs Manager
Sigalit Melcer, Manager, Clinical Trials Department
Ilan Miller, Intellectual Property and Medical Information Manager

Camargo Pharmaceutical Services, LLC

K. Gary Barnette, PhD, Vice President, Drug Development
Lisa Crose, PhD, Research Associate

(b) (4)

1.0 BACKGROUND

Dexcel Pharma Technologies (DPT) proposes development of omeprazole delayed-release, orally disintegrating tablets (ODT) for nonprescription (over-the-counter or OTC) treatment of frequent heartburn (occurring 2 or more days a week) in adults. DPT requested a Type B, pre-IND meeting with the Division of Nonprescription Drug Products by letter, dated June 17, 2015, and received on June 18, 2015. DPT is seeking FDA's input on their nonprescription drug product development program. FDA's Preliminary Comments were sent to DPT on October 5, 2015, and the meeting was held on October 6, 2015.

The sponsor's questions are in **bold** type, FDA's preliminary responses are in *italics*, and the discussion is recorded in normal font.

2.0 QUESTIONS

Regulatory/Medical

Question 1

DPT plans to submit a supplemental New Drug Application (sNDA) for addition of Omeprazole ODT formulation, 20 mg. The proposed ODT product has the same active ingredient and is intended for the same therapeutic indication: treatment of frequent heartburn. Does the agency agree that the sNDA regulatory pathway is appropriate for submission of the Omeprazole Delayed-release Orally Disintegrating Tablets?

FDA Preliminary Response Question 1

No, we do not agree. Delayed-release tablets and delayed-release, orally disintegrating tablets are two distinct dosage forms [see FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book), Appendix C]. Per the FDA "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees," different dosage forms should be submitted in separate original applications unless the products are identical in quantitative and qualitative composition.

Therefore, submit the proposed marketing application for the ODT dosage form as an original NDA.

Question 2

If the Agency requires the proposed product to be submitted as an NDA (rather than an sNDA), we intend to submit a 505(b)(2) application that relies on Dexcel's Omeprazole DR, approved as NDA 022032, as the sole listed drug. Does the Agency agree that, based on the demonstration of bioequivalence with the Omeprazole DR, the Sponsor can rely on NDA 022032 as the sole listed drug for a 505(b)(2) NDA for the proposed Omeprazole Delayed-Release Orally Disintegrating Tablets?

FDA Preliminary Response Question 2

No, we do not agree that NDA 022032 can be the sole listed drug relied upon for your planned 505(b)(2) application. An applicant may cross-reference a previously approved 505(b)(2) application for which it is the NDA holder to support approval of its new NDA, if scientifically appropriate.

If the cross-referenced portions of the applicant's previously approved 505(b)(2) application involve reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or published literature (as distinguished from any cross-referenced investigations that were conducted by or for the applicant or for which the applicant has obtained a right of reference or use), then the new NDA should be submitted pursuant to section 505(b)(2) of the FD&C Act. The applicant's new 505(b)(2) application should identify this/these listed drug(s) as relied upon for its new 505(b)(2) application in accordance with the Agency's regulations at 21 CFR 314.54. Note that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification/statement and notification), apply to each listed drug upon which an applicant relies.

In addition, we note that you intend to submit a published article by Allgood (2005) as supportive efficacy and safety data for your planned omeprazole delayed release, ODT application (see pages 21-24 of the meeting background package). The article by Allgood appears to describe a study with Prilosec OTC. As noted in the "505(b)(2) Regulatory Pathway" section below, reliance on published literature describing a listed drug(s) is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s). If you intend to rely, in part, on published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. An appropriate patent certification or statement with respect to any relevant patents that claim the listed drug(s) must also be provided.

Discussion:

Because both products consist of omeprazole base (rather than a salt formulation) and there is no FDA-approved ODT product, DPT intends to compare the proposed ODT product with their approved omeprazole delayed-release (non-ODT) product (NDA 022032). DPT's understanding was that their application would be submitted pursuant to section 505(b)(1) with respect to the data they own or have right of reference to from the omeprazole DR NDA 022032. However, FDA stated, and the sponsor acknowledged, that the proposed application is to be submitted

pursuant to section 505(b)(2) of the FD&C Act with Prilosec OTC identified as a listed drug because DPT's NDA 022032 relied upon the Agency's findings of safety and effectiveness for Prilosec OTC. FDA confirmed DPT's understanding.

Clinical Pharmacology

Question 3

Assuming bioequivalence is demonstrated between the proposed product and Omeprazole DR (NDA 022032) in the proposed bioequivalence study, is the bioequivalence study along with the bioavailability (food effect) study, sufficient as the registration trials for gaining an sNDA approval?

FDA Preliminary Response Question 3

Your proposed bioequivalence and bioavailability assessments are reasonable. However, to avoid potential biocreep issues, consider comparing your proposed ODT product with Prilosec OTC instead because efficacy in heartburn patients was established with the Prilosec OTC product for use in the over-the-counter (OTC) setting. Also, note preliminary response to Question 2 regarding submission of an original NDA.

Discussion:

DPT acknowledged that having Prilosec OTC as the reference product in the proposed BE study allows a direct comparison with the product that has the safety and efficacy data. DPT stated their preference to employ use of their own omeprazole DR product for the BE study rather than Prilosec OTC. FDA noted that there are recently identified safety signals related to proton pump inhibitor drugs (PPIs) as a class. In view of these relatively new safety signals, FDA expressed concern that the sponsor's choice of comparator may lead to potentially higher exposures due to biocreep, which could be a safety issue. FDA stated that, although it is not a requirement, use of Prilosec OTC as the reference product is encouraged. DPT acknowledged that they are aware of the risk of not including Prilosec OTC as the reference product. FDA stated that the issue of biocreep will be a matter for review upon submission of the NDA.

Question 4

If DPT demonstrates bioequivalence between the proposed Omeprazole ODT and Omeprazole DR (NDA 022032) when taken with and without water during the bioequivalence study under fasting conditions then DPT will only administer the drug product without water in the food effect bioavailability study. Does the Agency agree that the proposed product can be administered without water during the food effect study if bioequivalence is achieved during the bioequivalence study in both with and without water dosing conditions?

FDA Preliminary Response Question 4

Yes, we agree.

Question 5

If the proposed Omeprazole ODT drug product is determined to be bioequivalent with Omeprazole DR (NDA 022032), regardless of dosing condition (with or without water),

does the Agency agree with the proposed direction: “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”? Does the Agency agree that the direction listed above is acceptable provided that bioequivalence is established between the proposed product and Omeprazole DR (NDA 022032)?

FDA Preliminary Response Question 5

If the proposed omeprazole delayed-release ODT drug product is determined to be bioequivalent with omeprazole delayed-release tablet (NDA 022032), regardless of dosing condition (with or without water), the proposed second and third sentences "Place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water" may be acceptable if biocrep is not an issue. The acceptability of the proposed first sentence, “Take 1 tablet before eating in the morning,” would depend on the outcome of your food effect study. Final labeling is an application review issue.

Clinical

Question 6

All of the excipients that potentially might be in contact with the oropharyngeal cavity are known excipients that are listed in the IID for orally disintegration tablets, except for ascorbic acid which is listed in oral suspension. Safety justification for the repeat dosing of ascorbic acid, with data supporting its tolerability is summarized in the meeting package. Does the Agency agree that no additional safety studies will be required due to the excipients present in the proposed product, and that the information provided in the meeting package is sufficient to support 14-day dosing of the proposed drug product?

FDA Preliminary Response Question 6

Based on the details provided in the background material, we agree that no additional safety studies are required at this time. The results of your safety assessments conducted to evaluate the oropharyngeal cavity may determine whether additional studies are required. If you submit an NDA, include an Integrated Summary of Safety with an overall analysis of safety from your development program and a postmarketing safety assessment. We encourage you to request a pre-NDA meeting at the appropriate time for further discussion of the content and format of your NDA.

Discussion:

DPT acknowledged the requirement to include an Integrated Summary of Safety with an overall analysis of safety and a postmarketing safety assessment in the NDA. DPT agreed to provide summary safety information for the BE study, which was a small study consisting of healthy subjects. They also agreed that full safety datasets may be necessary if there appear to be patterns of adverse events in the oral cavity, serious adverse events, deaths or event-associated discontinuations. FDA and DPT agreed to discuss NDA content and format at a pre-NDA meeting.

Question 7

In order to support the safety of the new ODT formulation the Sponsor will conduct oropharyngeal examination before and after the dosing, in frame of the planned bioequivalence study. Does the Agency agree that oropharyngeal examination of three points (before dosing, 15 minutes after dosing, and before participants discharge) in each treatment arm during the BE/BA studies is sufficient to assess the effect of a new dosage form on oral cavity?

FDA Preliminary Response Question 7

Safety information in your NDA must support repeated use of your ODT formulation for the duration of treatment (14 days) in the OTC setting. Include information from your development program to support the safety of the ingredients in the drug product when administered as an ODT for 14 days. Whether the product is safe for use during the 14-day treatment period is a matter for review.

Discussion:

Referencing FDA's Question 6 response of "no additional safety studies are required at this time," DPT asked FDA to clarify their response regarding safety over the 14-day treatment period. FDA stated that no additional studies are required to address this issue; however, FDA asked DPT to provide a justification for the safety of their ODT formulation over the 14-day treatment period. FDA advised DPT to focus on any excipients that are novel to an ODT, such as ascorbic acid, and to provide data supporting the safe use of these excipients in the proposed product.

Nonclinical

Question 8

Does the Agency agree that no additional nonclinical studies will be required to support the sNDA of the proposed Omeprazole ODT product?

FDA Preliminary Response Question 8

You may rely on the FDA's previous findings of safety for the nonclinical portion of your NDA. The additional information that was provided in Appendix 3 of your meeting package for ascorbic acid will be evaluated during review of the NDA.

Labeling

Question 9

The proposed Omeprazole ODT contains only one flavor, which is a strawberry flavor. DPT plans to use the text "strawberry flavor" on the principal display panel. Does the Agency agree with the proposed "strawberry flavor" text?

FDA Preliminary Response Question 9

The proposal to use the text "strawberry flavor" on the principal display panel appears acceptable. However, a final determination is made during review of the NDA.

Chemistry, Manufacturing, and Controls (CMC)**Question 10**

Does the agency agree that the application will include 3 registration batches with 9 months stability data, and the sponsor will submit the stability data for 12 months, 4 months later as part of the safety update?

FDA Preliminary Response Question 10

We strongly recommend a complete application with 12-month long-term stability data at the time of submission of your NDA. The expiration date of the drug product will be a review issue and will be assessed according to ICH Q1E. We remind you that an amendment to include stability data as you have outlined above may or may not be acceptable based on the timelines of submission and Good Review Management Principles and Practices (GRMP) guidelines.

Discussion:

DPT and FDA agreed that 12-month stability data must be submitted no later than the time of submission of the 120-day safety update. Expiry can be extrapolated, according to ICH Q1E, if there are no significant trends on stability.

Additional Biopharmaceutics Comments:

1. Provide data for the justification of ODT designation. Refer to **Guidance for Industry: Orally Disintegrating Tablets** (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070578.pdf>) for related requirements and recommendations.
2. Conduct the in vitro alcohol dose-dump study first, with the highest strength of your proposed drug product. You may have to follow up with an in vivo alcohol dose-dumping pharmacokinetic study, depending on the results of the in vitro testing. Discuss the results of your in vitro study with FDA prior to the NDA submission.
 - a. The following alcohol concentrations for the in vitro dissolution studies (using 12 units/test) are recommended: 0%, 5%, 10%, 20%, and 40%.
 - b. Generally, the above range of alcohol concentrations in 0.1 N HCl and in the proposed dissolution medium is recommended. If the optimal dissolution medium has not been identified, then dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
 - c. Report f_2 values to assess the similarity (or lack thereof) in the dissolution profile comparisons.
 - Compare the shape of the dissolution profile to see if the modified release characteristics are maintained, especially in the first 2 hours.

- *In the report, include the complete data (i.e., individual, mean, SD, comparison plots, f_2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose-dumping study.*
3. *Additionally, we have the following advice regarding the dissolution information to be provided in your NDA.*
- a. ***Dissolution Test:*** *Include the dissolution method development report supporting the selection of the proposed dissolution test. Include the following information in the dissolution report:*
- i. *Solubility data for the drug substance covering the pH range.*
 - ii. *Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters used to select the proposed dissolution method as the optimal test for your product (i.e., selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.). If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. Clearly specify the testing conditions used for each test. Provide a complete dissolution profile covering at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. Use at least twelve samples per testing variable.*
 - iii. *The complete dissolution profile data (individual, mean, SD, profiles) for your product. Report the dissolution data as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim).*
 - iv. *Detailed batch information on your drug product employed in the study (i.e., Batch/Lot No., Manufacturing Date, Manufacturing Site, Expiration Date, Testing Date, Batch Size, etc.). Complete information on the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).*

You may also provide the dissolution method development report for review and comments under your IND.

- b. ***Dissolution Acceptance Criteria:*** *For the selection of the dissolution acceptance criteria of your product, provide the following:*
- i. *Use the dissolution profile data from the clinical batches and primary (registration) stability batches for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).*
 - ii. *Encompass the timeframe, for the in vitro dissolution profile, over*

- which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
- iii. *Establish delayed-release (enteric coated) product specifications in both acid stage and buffer stage per USP.*
- **Acid Stage:** *No individual tablet exceeds 10% dissolved at 2 hours.*
 - **Buffer Stage-IR:** *For immediate release, the selection of the specification time point X should be where Q=80% dissolution/release occurs.*
 - **Buffer Stage-ER:** *For extended release, set the establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data. Base the specification ranges on the overall dissolution data generated at these times. In general, the selection of the dissolution specification ranges is based on mean target value $\pm 10\%$ and NLT 80% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved/established In Vitro-In Vivo Correlation (IVIVC) model.*
- iv. *Set the dissolution acceptance criteria in a way to ensure consistent performance from lot to lot and these criteria are not to allow the release of any lots with dissolution profiles outside those that were tested clinically.*

Note that the final determination on the acceptability of the proposed acceptance criteria for your product will be made during the NDA review process based on the provided data.

ADDITIONAL ADMINISTRATIVE COMMENTS

LABELING REGULATIONS AND GUIDANCES

As you develop your label and labeling, we call your attention to the following pertinent labeling regulations and guidances:

Regulations under the Code of Federal Regulations (CFR)

When you prepare your NDA for submission to FDA:

1. Include all of the proposed labels and labeling (i.e., all count sizes with immediate container and carton labeling, including samples, and consumer information leaflet if proposed) as required under 21 CFR 314.50.
 - a. “Clean” labeling and marked up labeling (i.e., annotated) defining the information in the summary and technical sections of the application that support the inclusion of each statement in the proposed labeling.
 - b. Font and format specified under 21 CFR 201.66 as part of the annotated labeling or detailed in a separate document.

2. In addition to adhering to the format and content requirements for over-the-counter (OTC) drug product labeling (21 CFR 201.66), adhere to the following:
 - a. 21 CFR, Part 201 Subpart A-General Labeling Provisions and
 - b. Subpart C-Labeling Requirements for Over-the-Counter Drugs, which provides the labeling required for packaging (Principal Display Panel (PDP)-21 CFR 201.60 and statement of identity- 21CFR 201.61 etc.).

Guidances

1. See “Guidance for Industry– Labeling OTC Human Drug Products –Questions and Answers” (December 2008) for assistance with OTC labeling development.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078792.pdf>
2. In addition to submitting your label using the Structured Product Labeling (SPL) format, we recommend that you formally submit your proposed labeling in portable document format (PDF) electronically to your NDA.
 - a. To ensure electronic storage, retrieval, and viewability of the submitted labeling, which are often oversized and complex documents (i.e., OTC labeling usually has complex graphics and large file size), follow FDA’s portable document format (PDF) specifications detailed in the document found at the following URL:
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf>
 - b. For complete information on preparing your electronic submissions refer to the following URL:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>
 - c. Questions and general information regarding the preparation of submissions in electronic format may be directed to CDER at esub@fda.hhs.gov.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency’s

interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For

clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

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

/s/

KAREN M MAHONEY
11/03/2015