CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209400Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 209400
Review # 1

Drug Name/Dosage Form	Omeprazole Delayed Release Orally disintegrating tablets
Strength	20 mg
Route of Administration	Oral
Rx / OTC Dispensed	OTC
Applicant	Dexcel Pharma Technologies Ltd. 1 Dexcel St., Or-Akiva, Israel 3060000
US agent, if applicable	Jeanne M Novak, Ph.D., CBR International Corp., 2905 Wilderness Place, Ste. 202, Boulder, CO 80301

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	06-Sept-2016	ONDP/OPF/FR
Response to quality IR	21-Oct-2016	ONDP
Response to quality IR	16-Dec-2016	ONDP
Response to quality IR	14-Mar-2017	OPF/ONDP
CMC Information Request/ Changes in API Manufacturing	28-Mar-2017	OPF/ONDP
CMC Information Amendment/ Updated Batch Analysis	29-Mar-2017	OPF
Response to quality IR	28-April-2017	OPF

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Friedrich Burnett, Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI
Process	Krishnaiah Yellela, Ph.D.	OPF/DPAII/BranchVI
Microbiology	Krishnaiah Yellela, Ph.D.	OPF/DPAII/BranchVI
Facility	Carl Lee,	OPF/DIA/B3
Biopharmaceutics	Lee Hansong, Ph.D.	ONDP/DB/BBII
Regulatory Business Process Manager	Thao, Vu	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-II/ Branch VI
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	ORA/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Elise Luong, Ph.D.	ONDP/DNDP-II/ Branch VI

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	04/13/2012	Adequate
	Type IV			Adequate	N/A	Sufficient data in the application.
	Type IV			Adequate	Reviewed by J. Vidra, Ph.D. on 3/29/13	Review supported NDA (b) (4)
	Type III			Adequate	N/A	Sufficient data in the application.
	Type III			Adequate	Reviewed by Craig Bertha, Ph.D. on 12/13/12	Review supported NDA (b) (4)
	Type III			Adequate	N/A	Sufficient data in the application.
	Type III			Adequate	N/A	Sufficient data in the application.
	Type III			Adequate	N/A	Sufficient data in the application.

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			

Table of Contents

Executive Summary (NDA-209400)

I. Recommendations

Regarding Chemistry Manufacturing and Controls, the application may be approved.

A. Recommendation and Conclusion on Approvability

Regarding quality aspects of the application the drug substance, drug product, quality biopharmaceutics, microbiology, process and facility sections are reviewed and found adequate to support the approval of the application. The drug product has been granted a shelf life of 24 months under controlled room temperature storage conditions.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

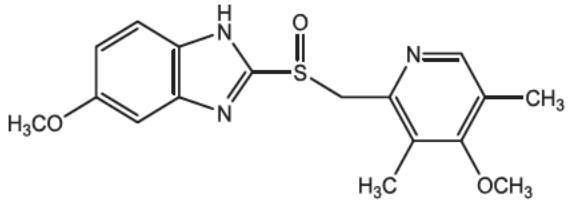
II. Summary of Quality Assessments;

Drug substance (Omeprazole) information is referred to a Type II DMF# (b) (4) The current status of the DMF is adequate and last reviewed on 11/03/2016. Some basic information is shown below.

1. Drug Substance [USAN Name] Quality Summary

Name (USAN): Omeprazole

Chemical Name: (IUPAC): 5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl}-1H-bensimidazole
Or
5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-yl) methyl]sulphinyl]-1*H*-benzimidazole
CAS number: 73590-58-6



Molecular Formula: $C_{17}H_{19}N_3O_3S$
Molecular Weight: 345.42

Omeprazole is a white to almost-white powder that is practically insoluble in water, sparingly soluble in in methanol and alcohol. Omeprazole exists as a racemic mixture of the two isomers 'R' and 'S'. Specifications for the drug substance meet all Omeprazole USP requirements regarding Identification and Organic impurities. In addition, particle size and residual solvents are controlled in the drug substance (see drug substance review pages 8-9). Following an IR letter, the DMF holder (b) (4) has conducted Elemental Impurities testing using ICP-OES on three validation batches of Omeprazole and data was found adequate.
Drug substance manufacturing facility (b) (4) was recommended for 'withhold' because of significant GMP deficiencies that were reported on the inspection that ended in (b) (4) and a pOAI alert was entered in Panorama. The form FDA 483 was issued with 4 observations. One of the observations (see facility review) states that (b) (4)

(b) (4) The firm (b) (4) responded to the observations and the subject matter was discussed (b) (4) with the Office of Surveillance (OS), Office of Compliance (OC), Drug Shortage Stuff (DSS), Office of Pharmaceutical Quality (OPQ) and Office of Regulatory Affairs (ORA). (b) (4) indicated that they have introduced (b) (4) corrective action. Based on the corrective action, it was decided that CDER OS will remove the pOAI alert from the Panorama and OPQ facility review can be completed with "acceptable" recommendation. Facility review with "acceptable recommendation" is completed on (b) (4) (b) (4)

(b) (4)

A. Drug Product [Omeprazole] Quality Summary

1. Strength: 20 mg

2. Description/Commercial Image:

Omeprazole 20 mg delayed release orally disintegrating tablet for over-the-counter (OTC) use is indicated for treatment of frequent heartburn (occurring two or more days a week). NDA 209400, a 505(b)2 application is relying on the safety and efficacy information from reference listed drug Prilosec OTC (omeprazole; AstraZeneca NDA 21229), in conjunction with information from the public domain. Omeprazole DR ODT tablet is reddish mottled uncoated tablet; embossed "20" on one side. The theoretical tablet weight is approximately 336 mg based on a yield corresponding to 100%.

***3.* Summary of Product Design**

This new dosage form of omeprazole, Omeprazole DR ODT is an orally disintegrating tablet containing 20 mg of omeprazole. Omeprazole is acid labile and therefore provided as enteric coated pellets and the tablets will disintegrate within a minute, when placed under the tongue. The patients are allowed to drink water for pushing the pellets into stomach.

Omeprazole DR ODT is manufactured (b) (4) strawberry flavor are used in FDA approved products and adequate information is provided in the application.

The weight of Omeprazole ODT is 336 mg. The main ingredients are (b) (4) (b) (4) hypromellose phthalate (b) (4) (b) (4) mg, (b) (4) % of the total tablet weight), Omeprazole (20 mg, 6%), sugar spheres ((b) (4) mg, (b) (4) %), crospovidone (~ (b) (4) mg,

(b) (4)%), microcrystalline cellulose ((b) (4) mg, (b) (4)%), amino methacrylate copolymer ((b) (4) mg, (b) (4)%) and Straw berry flavor (b) (4) of the total ODT weight. Crospovidone functions as a (b) (4) The excipients used in Omeprazole DR ODT, 20 mg, are within the levels listed in the FDA Inactive Ingredient Database (IID).
The Applicant accepted the Agency's recommendations about specification of acid stage from "No less than (b) (4)% in 120 minutes" to "No more than (NMT) (b) (4)%" release in 120 minutes" (see biopharmaceutics review page 4). The dissolution specification "NLT (b) (4)% (Q) in 30 minutes" for the drug product is found acceptable.

4. List of Excipients:

Amino methacrylate copolymer, ascorbic acid, cetyl alcohol, colloidal silicon dioxide, crospovidone, ferric oxide, flavor, hypromellose, hypromellose phthalate (b) (4), maize maltodextrin, mannitol, microcrystalline cellulose, propylene glycol, silicon dioxide, sodium stearate, sodium stearyl fumarate, sorbitol, sucralose, sugar spheres, (b) (4) (b) (4) talc, titanium dioxide, triethyl citrate.

5. Process Selection (Unit Operations Summary)

The key manufacturing process steps are: (b) (4) The control strategy for each process step is included and deemed adequate (see process review). The firm stated that future commercial batches will be manufactured using equipment from the same class. The BMR provided for the intended commercial batches are in line with the proposed Manufacturing Process and Controls.
The firm has submitted a Comparability Protocol as part of this submission (NDA 209400) that supports examining (b) (4) as annual reportable, (b) (4)

6. **Container Closure**:

The Omeprazole DR ODT is packed in (b) (4) blister and HDPE bottle. (b) (4) blister comprised of (b) (4) Each blister contains 7 or 14 tablets. The tablets are available in 14, 28, and 42 blister cartons, for 1, 2, and 3 courses of treatment respectively. Each pack for 1 course of treatment contains 14 tablets.
The bottle container closure is (b) (4) HDPE bottle and (b) (4) screw cap with a (b) (4). The container contains (b) (4). Each bottle is for 1 course of treatment and contains 14 tablets. Omeprazole DR ODT 20 mg are available in 1, 2, and 3 bottle cartons, for 1, 2, and 3 courses of treatment respectively.
The proposed package has (b) (4). For blister packaging, each tablet is individually sealed. The bottle container closure is HDPE bottle and (b) (4) screw cap with a (b) (4). The (b) (4) is a (b) (4), (b) (4).

7. Expiration Date & Storage Conditions

Proposed expiration date of the drug product of 24 months is acceptable based on the real time stability data obtained from 18-month study at long-term storage conditions (25°C/60% RH) and 6-month study at accelerated conditions (40°C/75% RH).
Proposed storage statement is "Store at 20°C – 25°C (68°F - 77°F); (b) (4) . However, during labeling negotiation it should be changed to "Store at 20°C – 25 C (68 F - 77°F); keep product out of high heat and moisture".

8. List of co-packaged components: None

B. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	None
Non Proprietary Name of the Drug Product	Omeprazole Delayed Release Orally Disintegrating Tablets
Non Proprietary Name of the Drug Substance	Omeprazole
Proposed Indication(s) including Intended Patient Population	Treats frequent heartburn (occurs 2 or more days a week)
Duration of Treatment	One tablet a day before eating in the morning; 14-Day course of Treatment; May repeat a 14-Day Courses every 4 months; Adults 18years of age and older.
Maximum Daily Dose	20 mg
Alternative Methods of Administration	None

C. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: II
   - Drug Product: II

2. Biowaivers/Biostudies
   - Biowaiver Requests: No
   - PK studies: Yes.

The submitted in vivo Bioavailability/Bioequivalence (BA/BE) studies (study# 150075 and study# 150076) are reviewed by the Office of Clinical Pharmacology (OCP).

- IVIVC: No

D. Novel Approaches

E. Any Special Product Quality Labeling Recommendations

Proprietary name of the drug product is not submitted. Label conformance to OTC product label requirements will be completed during labeling discussion with OND.
From quality review perspective below are few labeling recommendations.

1. Storage statement should be changed to "Store at 20°C – 25°C (68°F - 77°F); keep product out of high heat and moisture"

2. A statement "do not take this product with alcohol" is recommended by drug product reviewer.
3. Tamper-evident statement like "do not use if blister is damaged' and "sealed bottle for your protection" may be added if clinically relevant.

F. Life Cycle Knowledge Information (see table below)

Risk Assessment:

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	2	2	2	8	Method is validated and stability indicating. Impurities are monitored.
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Stable based on data provided.
Content uniformity	• Formulation • Raw materials • Process parameters •Scale/equipment • Site	3	2	2	12	(b) (4) [redacted] (b) (4)
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Controlled with specifications.

Dissolution	• Formulation • Raw materials • Process parameters •Scale/equipments • Site • Exclude major reformulations • Alcohol dose dumping	2	2	2	8	Method is based on "USP method for omeprazole delayed release capsule" and specification "NLT (b)(4)% in 30 min" is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Swapan K. De -S

Digitally signed by Swapan K. De -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Swapan K. De -S, 0.9.2342.19200300.100.1.1=1300132497
Date: 2017.05.23 08:23:01 -04'00'

Swapan De

Digitally signed by Swapan De
Date: 5/23/2017 08:26:54AM
GUID: 508da7220002a114329c9e07775b6e02

BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 209400

Drug Product Name / Strength: Omeprazole Delayed-Release Orally Disintegrating Tablet, 20 mg

Route of Administration: Oral

Applicant Name: Dexcel Pharma Technologies Ltd.

Review Summary:

The Listed Drug Prilosec® OTC [omeprazole magnesium, 20.6 mg (equivalent to 20 mg omeprazole) oral tablet, developed by AstraZeneca, was approved by FDA under NDA 021229 on 06/20/2003. It is indicated for the treatment of frequent heartburn.

Dexcel Pharma Technologies Ltd. developed Omeprazole Delayed-Release Orally Disintegrating Tablet (ODT), 20 mg for OTC use and submitted on 9/6/2016 the application under NDA 209400 referencing NDA 21229 and seeking approval from the Agency through 505(b)(2) pathway.

The Biopharmaceutics review focuses on the dissolution method, dissolution and disintegration data, dissolution and disintegration specifications, and in vitro alcohol induced dose dumping study.

The Applicant developed the dissolution method based on the USP method for Omeprazole delayed-release capsules for their proposed product, which is acceptable. The following proposed dissolution specifications are also found acceptable for implementation:

Acid stage: NMT (b)(4)% in 120 minutes
Buffer stage: NLT (b)(4)% in 30 minutes

The Applicant used USP <701> method to conduct the disintegration tests. The following disintegration specification has been set as agreed upon with the Applicant:
NMT (b)(4) seconds

In Vivo Alcohol-Induced Dose Dumping Testing shows that 40% of alcohol is likely to cause dose dumping of the proposed product. The Clinpharm Reviewer in the Office of Clinical Pharmacology (OCP) will be consulted for potential alcohol dose-dumping effect. The Applicant proposed the labeling that the product should not be taken with alcohol. The OCP will make a final decision if an in vivo alcohol dose-dumping pharmacokinetic (PK) study is needed or not.

From the Biopharmaceutics perspective, this Reviewer concludes that NDA 209400 for Omeprazole Delayed-Release Orally Disintegrating Tablet, 20 mg is ADEQUATE for approval.

List Submissions being reviewed (table):

Application 209400 - Sequence 0000 - 0000 (1) 09/06/2016 ORIG-1 /Multiple Categories/Subcategories
Application 209400 - Sequence 0003 - 0003 (4) 12/16/2016 ORIG-1 /Multiple Categories/Subcategories
Application 209400 - Sequence 0007 - 0007 (8) 03/14/2017 ORIG-1 /Quality/Response To Information Request

Module	Content
1.11.1	Quality information amendment- response to FDA information request dated 19 November 2016 Quality information amendment- response to FDA information request dated 21 February 2017
2.3.P	Quality overall summary - drug product
2.7.1	Summary of Bipharmacutic Studies
3.2.P.2	Pharmaceutical Development
3.2.P.5.1	Specifications
3.2.P.5.2	Analytical Procedure Disintegration DSNGEN03 Analytical Procedure Dissolution DISOME13
3.2.P.5.3	Validation of Analytical Procedures
3.2.P.5.4	Batch Analyses

Highlight Key Outstanding Issues from Last Cycle:

Concise Description Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment: The Applicant reported that it is a BCS II product, which has low solubility and high permeability.

Solubility: Soluble in Methylene chloride, Sparingly soluble in Alcohol, Sparingly soluble in Methanol and Very Slightly soluble in Water

Permeability: N/A

Dissolution: See the Biopharmaceutics review.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

I. Information Request (IR) 1

On 11/19/2016, the FDA sent the following IR to the Applicant. On 12/16/2016, the Applicant responded to the IR. The following are the IR, the Applicant's response, and Reviewer's assessment:

IR 1

1. You set the following specification at acid stage for your proposed product:

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

   It is easily confused as "Not less than (b) (4)% of the dissolved omeprazole label claim in 120 minutes". We recommend you to change it to "NMT (b) (4)% in 120 minutes" or "NLT (b) (4) % of the label claim remaining in 120 minutes".

2. Your proposed dissolution specification for buffer stage is not consistent throughout the whole submission. You proposed the specification "NLT (b) (4)% (Q) in 30 minutes" in the following documents:

   - 3.2.P.5.1 specifications
   - 3.2.P.5.6 Justification of Specifications
   - 3.2.P.2 Pharmaceutics development

   However, the Applicant set a different specification "NLT (b) (4)% (Q) in 30 minutes (or (b) (4) including acid stage)" in other documents:

   - 3.2.P.5.3 Val Analyte Proc Dissolution OMEP406R

- 3.2.P.5.4 Batch analyses

Clarify the discrepancy and make a necessary correction.

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 to the Agency for review.

The applicant's response to Item 1

The Applicant revised the specification of acid stage from "No less than (b) (4)% in 120 minutes" to "No more than (NMT) (b) (4)%" release in 120 minutes", and updated the relevant parts of this NDA accordingly.

Reviewer's comment

The response is adequate.

The applicant's response to Item 2

The Applicant stated that the discrepancy in the dissolution specification is a result of specifications life cycle. The correct proposed dissolution specifications are "NLT (b) (4)% (Q) in 30 minutes". The Applicant updated the relevant parts of this NDA accordingly.

Reviewer's comment

The response is adequate.

The applicant's response to Item 3

The Applicant stated that the complete disintegration data (individual, mean, SD, RSD) on 12 tablets are not collected in routine testing. The Applicant usually measures and reports the time it takes for the last tablet to disintegrate in compliance with USP <701>.

However, the Applicant collected the complete disintegration data from the samples stored for 24 months at 25°C/60% RH in either bottles or blisters, as per FDA recommendation. The data are reported in section 3.2.P.8.1 –Annex 2. Mean results per batch range from 10.5-14.5 seconds, and the RSD is less than 10%.

Based on the above data, the Applicant revised the specification of disintegration for stability testing from "NMT (b) (4) seconds" to "NMT (b) (4) seconds", and updated the relevant parts of this NDA accordingly.

Reviewer's comment

The response is adequate. The specification for disintegration will be thoroughly reviewed in the next section.

II. Dissolution method

The Applicant developed the following dissolution method for their proposed product based on the USP method for Omeprazole delayed-release capsules. The difference between two methods is that USP method only reports the specification at buffer stage, and the Applicant determined the drug release at buffer stage in one test (Table 1) and determined the drug release at acid stage in a separate gastric resistance test (Table 2).

Table 1. The Applicant's dissolution method for buffer stage

	The Applicant's method for buffer stage	USP method for Omeprazole delayed-release capsules
Apparatus	USP apparatus 2 (paddles)	USP apparatus 2 (paddles)
Speed	100 rpm	100 rpm
Dissolution media	Acid stage: 0.1 HCl Buffer stage: pH 6.8 buffer	Acid stage: 0.1 HCl Buffer stage: pH 6.8 buffer
Volume	Acid stage: 500 mL Buffer stage: 900 mL	Acid stage: 500 mL Buffer stage: 900 mL
Sampling times	Buffer stage: (b) (4) 30 minutes	30 minutes
Temperature	37 ± 0.5 °C	37 ± 0.5 °C
Specification	Buffer stage: No less than (NLT) (b) (4) % (Q) in 30 minutes	No less than (NLT) 75% (Q) in 30 minutes

Table 2. The Applicant's dissolution method for acid stage

	The Applicant's method for acid stage

	(b) (4)
Apparatus	
Speed	
Dissolution media	
Volume	
Sampling time	
Temperature	
Sample preparation	
Specification	

III. The Analytical method for dissolution

The applicant used HPLC with UV detection to determine the concentrations of the dissolution samples. The UV detection wavelength was set at 280 nm. The percentage of drug release is calculated using the following equations:

Acid stage:

Omeprazole release (%)= 100% - % assay after 2 hours under acidic condition

Buffer stage:

$$\text{Omeprazole released (\%)}: \frac{A_{sa} \times W_{st} \times 900 \times D_{sa} \times C_{st} \times 100}{A_{st} \times D_{st} \times LC}$$

Where:
Asa = peak area of Omeprazole in sample solution
Ast = peak area of Omeprazole in standard solution
Wst = weight of Omeprazole amount in standard solution (mg)
900 = volume in buffer stage.
Dsa = dilution of sample solution
Dst = dilution of standard solution
Cst = content of in house standard (in case of 100%, Cst = 1)
LC = labeled Omeprazole content of tablets (mg/tablet)
100 = convers ion factor to percent

Table 3. Chromatographic Parameters

Parameter	USP method	NDA 209400
Column	C8, 4.0 mm x 12.5 mm, 5 µm	BetaBasic RP-8, 5µ, 150x4.6mm
Flow rate	1.0 mL/min	1.0 mL/min
Detector	280 nm	280 nm
Injection volume	20 µL	20 µL
Runtime	Not reported	Not reported
Column temperature	Room temperature	Room temperature
Mobile phase	340 mL of Acetonitrile volumetrically dilute with Buffer phosphate pH 7.6 to 1000 mL	340 mL of Acetonitrile volumetrically dilute with Buffer phosphate pH 9.0 to 1000 mL

It should be noted that the Applicant used different mobile phase for HPLC analysis. Initially, the Applicant employed the USP recommended mobile phase, but poor chromatography (poor resolution) was observed. When pH of mobile phase was increased from 7.6 to 9.0, omeprazole peak resolution was significantly improved.

IV. Dissolution method development

A. The dissolution method for buffer stage

(b) (4)

(b) (4)

V. Validation of Analytical procedures for Dissolution

The analytical method for dissolution was validated in Dexcel Limited R&D. The validation includes specificity, linearity & range, accuracy, precision (repeatability and intermediate precision), stability in analytical solution, effect of filter variation, and robustness.

VI. Disintegration test method

The Applicant used USP <701> method to conduct the disintegration tests. The disintegration apparatus is Erweka ZT3-3 or equivalent.

VII. Dissolution and specification

The Applicant provided the complete dissolution data of Batches BY501014, BY470914, and BY680914-1 at acid stage and buffer stage. The data are listed in Appendixes for details.

Acid stage

The mean dissolution data at acid stage were summarized in Table 4, which are within the acceptance range. However, the Applicant just used six units for each batch to conduct dissolution tests, which failed to meet our expectation. Especially, Tablet 1 of Batch BY501014 has (b) (4)% release at acid stage, which made this batch fail to meet the specification of acid stage at Stage 1. The Applicant should have used six more units to continue the dissolution test to see if BY501014 can pass the specification at Stage 2, but Stage 2 test was not conducted. An IR was sent out to request the Applicant to clarify this issue.

Table 4. Mean dissolution data of test products at acid stage

Batch number/Time Points (min)	Mean dissolution at acid stage (120 min)
Batch BY501014	8%
Batch BY470914	5%
Batch BY680914-1	2%

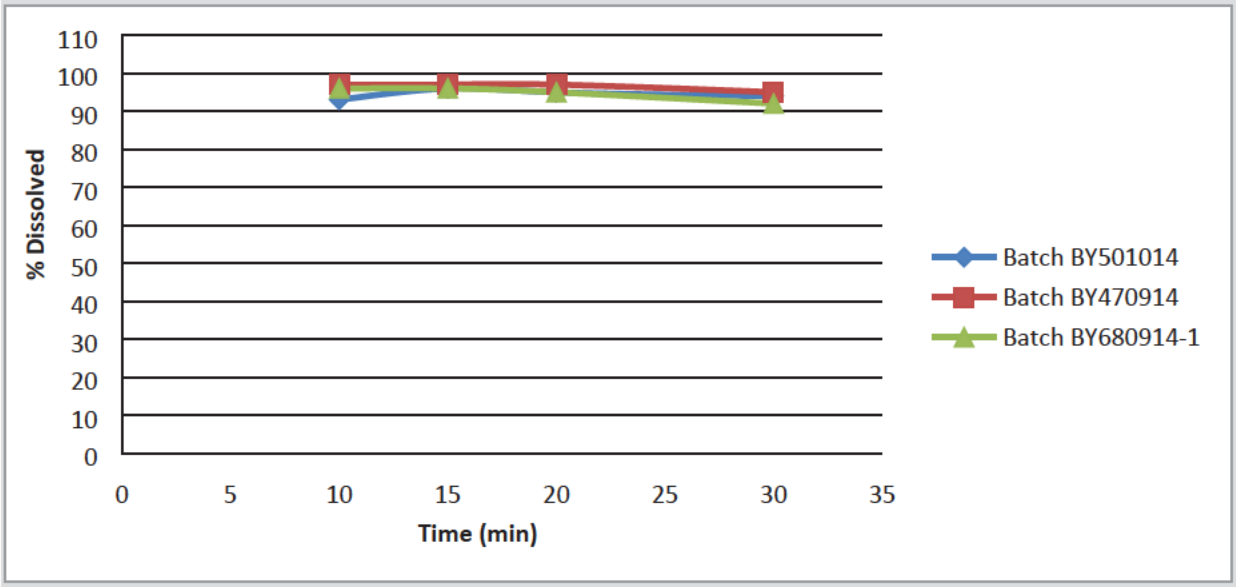
Buffer stage

Table 5. Mean dissolution data of test products at buffer stage

Batch number/Time Points (min)	10	15	20	30
Batch BY501014	93	96	95	94
Batch BY470914	97	97	97	95
Batch BY680914-1	96	96	95	92

The mean dissolution data at buffer stage were summarized in Table 5, which show that all three batches are able to meet the proposed specification: NLT (b) (4) % in 30 minutes.

Figure 1. Mean dissolution profile comparison at buffer stage



VIII. Disintegration data and specification

The Applicant provided the disintegration data of Batches BY501014, BY470914, and BY680914-1, which are listed in the following table. The results refer to the time it takes for the last tablet of each batch to disintegrate.

Table 6. the disintegration data of Batches BY501014, BY470914, and BY680914-1

Batch number	Disintegration time (seconds)
BY501014	17
BY470914	18
BY680914-1	15

In the response to IR 1, the Applicant stated that they conducted disintegration tests and collected the complete disintegration data on 12 tablets per batch, which were stored for 24 month at 25°C/60% RH in either bottles or blisters. The data are listed in Table 7.

Table 7. Complete stability disintegration data of Batches BY501014, BY470914, and BY680914-1 (both bottles and blisters)

Batch number	Disintegration, (sec), Acceptance Criteria: NMT (b) (4)												Mean (sec)	Rsd (%)	SD (%)
	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12			
BY470914 (b) (4) blister												(b) (4)	14.5	3.6	0.52
BY470914A HDPE bottle													13.3	8.0	1.07
BY680914-1 (b) (4) blister													11.6	5.8	0.67
BY680914A HDPE bottle													10.5	5.0	0.52
BY501014 (b) (4) blister													11.3	6.7	0.75
BY501014A HDPE bottle													12.9	5.2	0.67

Initially, the Applicant set different disintegration specifications for release and stability, respectively, which are shown below:

Test	Disintegration Specification
Release	NMT (b) (4) seconds
Stability	NMT (b) (4) seconds

However, in the response to IR 1, the Applicant tightened the disintegration specification for stability test from "NMT (b) (4) seconds" to "NMT (b) (4) seconds". The data listed in Tables 6 and 7 show that all batches are able to meet the proposed disintegration specification for both release and stability test.

It should be noted that the stability data show that all batches could not meet the specification "NMT (b) (4) seconds" when they were stored at 40 °C/75%RH for 6 months. This Reviewer consulted with the CMC reviewer and both concluded that it is acceptable.

IX. Information Request 2

On 2/21/2017, the FDA sent the following IR to the Applicant. On 3/14/2017, the Applicant responded to the IR. The following are the IR, the Applicant's response, and Reviewer's assessment:

IR 2

You just used six units from each batch to conduct dissolution tests at acid stage, which failed to meet our expectation. Especially, Tablet 1 of Batch BY501014 has dissolution of (b) (4) % at acid stage, which did not meet the specification of acid stage at Stage 1. You should have used six

more units to continue the dissolution test at acid stage to see if BY501014 can pass the specification at Stage 2.

Employ the redeveloped Gastric resistance method to reconduct the dissolution tests at acid stage, and submit the complete dissolution data(individual n=12 units/batch, mean, SD, RSD) to the Agency for review.

The Applicant's response to the IR 2

The Applicant clarified that only six units were used in the dissolution test at acid stage for release test and stability up to 12 months.

The specification of acid stage was set as "NLT (b)(4)% in 120 minutes" when the dissolution test at acid stage was on Batch BY501014 in November 2014. The specification of acid stage was tightened from "NLT (b)(4)% in 120 minutes" to "NLT (b)(4)% in 120 minutes" per FDA recommendation in the preliminary comments to the e-NDA (Dated May 06 2016).

In Addition, the Applicant optimized the gastric resistance method for the stability dissolution test. Specifically, the extraction time of the omeprazole in pH 10.0 phosphate buffer at 200 rpm was increased from (b)(4)minutes to (b)(4) minutes. The longer extraction time ensures omeprazole fully extracted from the pellets.

The Applicant used the new method to conduct the dissolution test at acid stage on 12 tablets of Batch BY501014 for stability (18 months and 24 months). The complete dissolution data are provided in Table 8, which show that Batch BY501014 is able to meet the specification "NLT (b)(4)% in 120 minutes" for both 18 months and 24 months testing at Stage 1 or Stage 2.

Table 8. Gastric resistance results; 25°C/60%RH 18 & 24 month intervals

Gastric resistance results; 25°C/60%RH			
	Time (Months)	(b) (4) blister -BY501014	HDPE bottle- BY501014A
Individual	18	(b) (4)	
Mean		4.1%	4.7%
RSD		85.8%	32.6%
SD*		3.55	1.53
Individual	24	(b) (4)	
Mean		5.0%	4.5%
RSD		33.2%	66.3%
SD*		1.66	2.98

*Calculated by RSD (rounded results) (b) (4) mean

Therefore, even though the dissolution test at acid stage of batch BY501014 was conducted on only 6 tablets up to the 12 month time point, it can be concluded that there is no concern that the product will fail to meet the current acceptance criteria.

Reviewer's comment

The response is acceptable. The dissolution test for release could not be repeated on Batch BY501014, because this batch is already expired. Since Batch BY501014 is able to meet the specification of acid stage for stability (18 months and 24 months) at Stage 2, it is very likely this batch should have passed the specification at Stage 2 if the Applicant used six more units to continue the dissolution test at acid stage.

Appendix I.

Dissolution results at acid stage for batch no. BY501014

	B.N.BY501014							
Time(min)	Tab 1 %	Tab 2 %	Tab 3 %	Tab 4 %	Tab 5 %	Tab 6 %	Mean %	RSD %
120	(b) (4)							

Dissolution results at buffer stage for batch no. BY501014

	B.N.BY501014													
Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10	Tab 11	Tab 12	Mean %	RSD %
130	(b) (4)													
135														
140														
150														

Appendix II

Dissolution results at acid stage for batch no. BY470914

	B.N.BY470914							
Time(min)	Tab 1 %	Tab 2 %	Tab 3 %	Tab 4 %	Tab 5 %	Tab 6 %	Mean %	RSD %
120	(b) (4)							

Dissolution results at buffer stage for batch no. BY470914

	B.N.BY470914													
Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10	Tab 11	Tab 12	Mean %	RSD %
130	(b) (4)													
135														
140														
150														

Appendix III

Dissolution results at acid stage for batch no. BY680914-1

	B.N.BY680914-1							
Time(min)	Tab 1 %	Tab 2 %	Tab 3 %	Tab 4 %	Tab 5 %	Tab 6 %	Mean %	RSD %
120	(b) (4)							

Dissolution results at buffer stage for batch no. BY680914-1

	B.N.BY680914-1													
Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10	Tab 11	Tab 12	Mean %	RSD %
130	(b) (4)													
135														
140														
150														

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: N/A

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: N/A

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment:

The Applicant used the QC method to conduct the in vitro alcohol induced dose dumping tests in 0.1 N HCl containing 0%, 5%, 10%, 20%, and 40% (v/v) ethanol, respectively. The following shows how 0.1 N HCl was mixed with alcohol to prepare the dissolution medium:

- 0% Alcohol (500 mL HCl 0.1N)
- 5% Alcohol (25 mL ethanol, 475 ml HCl 0.1N)
- 10% Alcohol (50 mL ethanol, 450 ml HCl 0.1N)
- 20% Alcohol (100 mL ethanol, 400 ml HCl 0.1N)
- 40% Alcohol (200 mL ethanol, 300 ml HCl 0.1N)

Table 9. Dissolution Method for Alcohol Dose Dumping Evaluation

Apparatus	USP apparatus 2 (paddles)
Speed	100 rpm
Dissolution media	0.1 N HCl with X% alcohol
Volume	500 mL
Sampling times	30, 60, 90, and 120 minutes
Temperature	37 ±0.5 °C

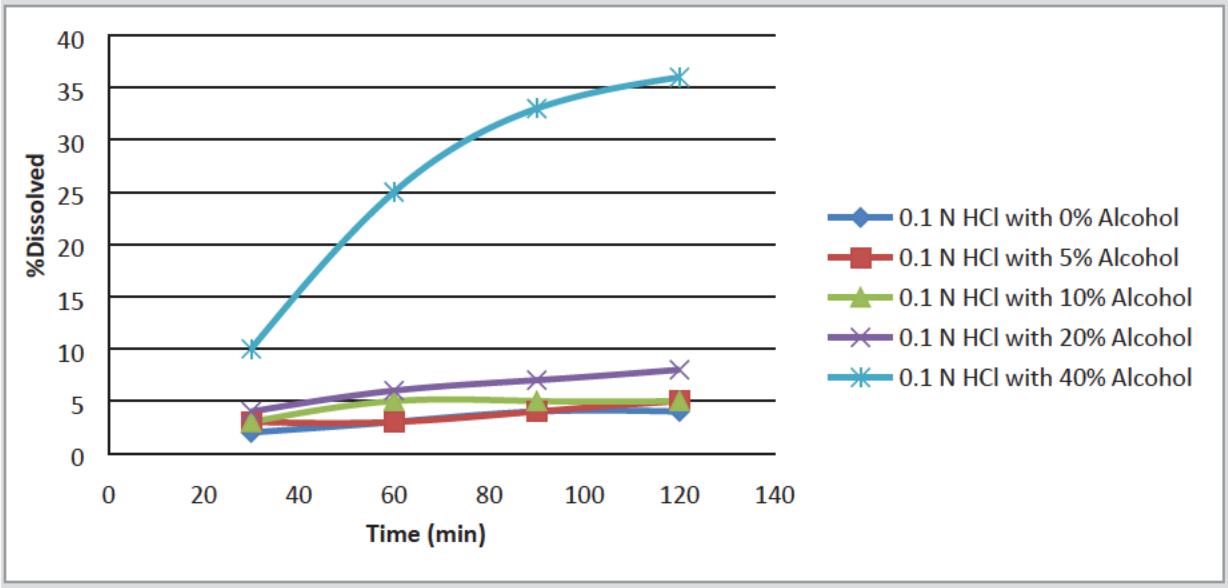
Batch BY501014 (bio batch) was used for this study. The mean dissolution data are summarized in Table 10.

Table 10. Result Summary of Alcohol–induced Dose-Dumping Study

Dissolution medium/Time (min)	30	60	90	120
0.1 N HCl with 0% Alcohol	2	3	4	4

0.1 N HCl with 5% Alcohol	3	3	4	5
0.1 N HCl with 10% Alcohol	3	5	5	5
0.1 N HCl with 20% Alcohol	4	6	7	8
0.1 N HCl with 40% Alcohol	10	25	33	36

Figure 4. Comparative Dissolution Profile of the tablets from Batch BY501014 in 0.1N HCl Containing 0%, 5%, 10%, 20% and 40% Alcohol



This Reviewer calculated the similarity factors between the dissolution profiles of Omeprazole Delayed-Release Orally Disintegrating Tablet in the dissolution medium without alcohol and those generated in medium with certain amount of alcohol, and the f2 values are listed in Table 11. The results demonstrate that 40% of alcohol is likely to cause dose dumping of Omeprazole Delayed-Release Orally Disintegrating Tablet.

Table 11. The similarity factors between the proposed product's dissolution profiles in medium without alcohol and medium with x% of alcohol

Comparison	F2 values
0.1 N HCl with 0% of alcohol vs. 0.1 N HCl with 5% of alcohol	95.60
0.1 N HCl with 0% of alcohol vs. 0.1 N HCl with 10% of alcohol	89.02
0.1 N HCl with 0% of alcohol vs. 0.1 N HCl with 20% of alcohol	74.47

0.1 N HCl with 0% of alcohol vs. 0.1 N HCl with 40% of alcohol	30.47

The Applicant stated that co-administration with higher concentrations of alcohol will have an impact on the efficacy, but not on the safety of the drug. In order to reduce the risk of lack of efficacy, the Applicant has proposed clear instructions in the labeling that the product should not be taken with alcohol.

In the meantime, the Applicant submitted a biowaiver request for In Vivo Alcohol-Induced Dose Dumping Testing. The Clinical Pharmacology reviewer addressed this issue.

Reviewer's comment:

In Section 3.2.P.2. Alcohol Induced Dose Dumping Study Report, the Applicant stated they used the following method to calculate the percentage of omeprazole in the study:

$$\text{Omeprazole released (\%)} = \frac{A_s \times W_{st} \times V \times P}{A_{st} \times K} \times 100$$

Where,
As = absorbance of sample solution
Ast = absorbance of standard solution
Ws1 = concentration of Omeprazole in house standard (mg/ml)
K = content (in mg) of active ingredient per tablet
V = volume of dissolution medium (ml)
P = content of Omeprazole in house standard (in case of 100%, P= 1.0)

It is known that omeprazole is not stable in 0.1 N HCl; therefore, the above method cannot accurately measure the concentration of omeprazole released from the drug product during the alcohol induced dose dumping study. The Applicant's reported results have reference value only.

Because the whole dissolution profiles have to be determined during the test, the gastric resistance method developed for quality control cannot be applied here. So far, a more appropriate method has not been reported.

As the Applicant has already labelled that the product should not be taken with alcohol, it is not crucial to figure out if the dissolution method can accurately determine that alcohol can cause the dose dumping of the proposed product in vitro or not.

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: N/A

Bridging of Formulations

Reviewer's Assessment:

The formulation of the commercial batches is the same as that of exhibit batches. The scale-up batch size of the commercial batches is not more than (b) (4) that of the exhibit batches.

Biowaiver Request

Reviewer's Assessment: N/A

R Regional Information

Comparability Protocols

Reviewer's Assessment:

Post-Approval Commitments

Reviewer's Assessment:

Lifecycle Management Considerations

List of Deficiencies:

Primary Biopharmaceutics Reviewer Name and Date:

Hansong Chen, Pharm.D, Ph.D., 4/28/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Tien-Mien Chen, Ph.D., 5/4/2017

Acting Biopharmaceutics Lead

DBBII/DB/ONDP/OPQ

Hansong Chen

Digitally signed by Hansong Chen
Date: 5/04/2017 11:41:19AM
GUID: 525d7d660003845a197a2e1682433d0d

Tien Mien Chen

Digitally signed by Tien Mien Chen
Date: 5/04/2017 01:29:12PM
GUID: 508da7240002a26723d38018ce005126

Swapan De

Digitally signed by Swapan De
Date: 5/23/2017 08:42:00AM
GUID: 508da7220002a114329c9e07775b6e02

OPQ Filing Review NDA-209400

Dexcel Pharma Technologies Limited.

Omeprazole Delayed Release Orally Disintegrating Tablets, 20 mg

505 (b)(2)

DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED? Yes

Drug Substance:

Omeprazole, USP

Drug Master File (DMF) (b) (4) The manufacturer of Omeprazole, USP is (b) (4) (b) (4).

Two facilities are listed in the DMF. However, the applicant confirmed (October 14, 2016) that only one site (FEI# (b) (4) will be used for the manufacture of drug substance, Omeprazole USP.

Same API approved for Omeprazole DR, 20 mg tablets (NDA 022032, Dexcel Pharma Technologies Ltd, refers to as "DPT").

Elemental Impurities (ICH Q3C):

IR question: Replace the test for Heavy Metals USP<231> with the test for Elemental Impurities (USP<232> and USP<233> and follow the guidelines for reporting of individual metals such as (b) (4).

Response October 14, 2016: Applicant will update test method for elemental impurities according to USP<232> and <233> and report individual metal impurities.

Drug Product:

Omeprazole Delayed Release Orally Disintegrating Tablets 20mg (Referred to as "Omeprazole ODT") are round reddish mottled uncoated tablets, embossed with "20" on one side. The tablets are packaged in one of two configurations: HDPE bottles with (b) (4) or (b) (4) (b) (4) blisters. Each pack for one course of treatment contains 14 tablets for 14 day course of treatment.

All the excipients, except for (b) (4) and the Strawberry flavor mixture are USP/NF compendia ingredients. These excipients are used in recently approved NDA 208025 (Dexcel Pharma Tech.)

Stability data: Results of 18 months long-term stability studies for three batches are provided. A shelf-life of 24 months is proposed.

IR question: Update "function" column of Table 1 in section 3.2.P.3.1 to clearly describe whether Dexcel Ltd. (Akiva, Israel), is performing release, stability (for bulk and packaged drug products) as well as other quality testing for the drug product.
Response October 14, 2016: Updated response is included to clearly state that the site will perform all quality testing including stability studies.

IR question on manufacturing process and controls section): Part of section 3.2.P.3.3 is not readable due to unusual font. Submit an updated and translated section of 3.2.P.3.3 for review.
Response October 14, 2016: Section is updated and original Hebrew is translated to English.

Biopharmaceutics:
IR for 74-day letter:

1. You set the following specification at acid stage for your proposed product:

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

   It is easily confused as "Not less than (b) (4) % of the dissolved omeprazole label claim in (b) (4) We recommend you to change it to "NMT (b) (4) % dissolved in (b) (4)"

2. Your proposed dissolution specification for buffer stage is not consistent throughout the whole submission. You proposed the specification "NLT (b) (4) % (Q) in 30 minutes" in the following documents:

   - 3.2.P.5.1 specifications
   - 3.2.P.5.6 Justification of Specifications
   - 3.2.P.2 Pharmaceutics development

   However, the Applicant set a different specification "NLT (b) (4) % (Q) in 30 minutes (b) (4) " in other documents:

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

   Clarify the discrepancy and make a necessary correction.

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 to the Agency for review.