CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208025Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:
NDA: Approval /Complete Response
ANDA: Approval/ Complete Response-Minor/ Complete Response - Major

NDA 208025
Review #2 (Resubmission)

Executive Summary

A. Biopharmaceutics Considerations

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

   Note: In Module 2.3.P, the Applicant indicated that "API is BCS class II (characterized by low solubility and high permeability). In Module 3.2.P.2, the Applicant indicated that "Lansoprazole DR ODT 15 mg contains the active ingredient lansoprazole, which is classified as BCS Class II".

2. Biowaivers/Biostudies
   - Biowaiver Requests: No Biowaiver request submitted
   - PK studies: The submitted in vivo Bioavailability/Bioequivalence (BA/BE) studies (study# 120383 and study# 120384) are reviewed by the Office of Clinical Pharmacology (OCP).
   - IVIVC: No IVIVC submitted

ASSESSMENT OF THE BIOPHARMACUETICS

BACKGROUND

The Applicant, Dexcel Pharma Technologies Ltd, submitted this original **NDA 208025** on 12/05/2014 for their proposed drug product, Lansoprazole Delayed-Release Orally Disintegrating Tablets (DR ODT), 15 mg. It is indicated to treat frequent heartburn (occurs *2 or more* days a week), but not intended for immediate relief of heartburn; this drug may take1 to 4 days for full effect.

This submission is a 505(b)(2) application referring the listed drug (LD) Prevacid 24HR®, (lansoprazole delayed release capsules, 15 mg) which was approved under NDA 022327 on 05/18/2009.

On 02/06/2015, FDA issued a Refused to File (RTF) letter to this NDA due to clinical issues. On 08/05/2015, the Applicant resubmitted this NDA 208025 and provided responses to the RTF comments.

For this resubmission, the Division of Biopharmaceutics focuses on the reviewing of:

- In vitro dissolution test and acceptance criteria of the proposed drug product;
- In vitro alcohol dose dumping studies of the proposed drug product.

BIOPHARMACEUTICS ASSESSMENT

1. The composition of proposed drug product formulation

The proposed drug product is uncoated tablets, comprised of (b) (4) coated pellets containing the active substance, Lansoprazole. The unit composition of the (b) (4) coated pellets is provided in Table 1. The final (b) (4) tablet formulation is provided in Table 2.

Table 1: Unit Composition of (b) (4)-coated Pellets

Ingredient	Weight per tablet (mg)	Function	Quality Standard
(b) (4)			
Lansoprazole	15.00	Drug substance	USP
Mannitol		(b) (4)	USP
Meglumine			USP
Polysorbate 80			NF
Hypromellose (b) (4)			USP
(b) (4)			
Talc			USP
(b) (4)			USP
Hypromellose Phthalate (b) (4)			NF
Cetyl Alcohol			NF
Triethyl Citrate			NF
(b) (4)			USP
Titanium Dioxide			USP
(b) (4)			NF[2]
			USP
Total weight (b) (4) coated Tablets			(b) (4)

Table 2: Lansoprazole DR ODT 15 mg, Final Tablet Composition

Ingredient	Weight per tablet (mg)	Function	Quality Standard
(b) (4)			
		(b) (4)	
Crospovidone			NF
Sucralose			NF
Ascorbic Acid			USP
Strawberry flavor (b) (4)			DMF holder standard
Colloidal Silicon Dioxide			NF
Sodium Stearyl Fumarate			NF
Total tablet weight	248.0		

Reviewer's Assessment:

The submitted in vivo Bioavailability/Bioequivalence (BA/BE) studies (study# 120383 and study# 120384) are under reviewing by the Office of Clinical Pharmacology (OCP).

In RTF letter, No.3 review issue was:

> *3. Pending a thorough review, it appears that significant dose-dumping of lansoprazole occurred in the presence of 40% alcohol based on in vitro studies. Comment on the clinical relevance of this finding, and your specific plans to*

address this concern for your proposed OTC drug product.

To address this issue, the Applicant provided new in vitro alcohol dose dumping data (in M.2.7.1), and submitted the **Waiver of In Vivo Alcohol-Induced Dose Dumping Testing** (in M.1.12.15). The Division of Biopharmaceutics (DB) will review the in vitro alcohol dose dumping study and data, the Office of Clinical Pharmacology (OCP) will review the waiver request.

2. The proposed in vitro dissolution method

(1) In vitro dissolution method development

The originally proposed in vitro dissolution method and acceptance criteria for drug product, Lansoprazole DR ODT, 15 mg, are summarized in Table 2. This dissolution method was adapted from the USP and FDA both recommended method for Lansoprazole delayed-release tablet, but changed the rotation speed from recommended 75 rpm to the proposed (b) (4) rpm (from M.3.2.P.2).

Table 2: Original proposed in vitro dissolution parameters and specification for Lansoprazole DR ODT, 15 mg (from 3.2.P.2)

Acid Stage:	
Apparatus:	II (Paddle)
Medium:	0.1 N Hydrochloride Acid (HCl)
Volume:	500 mL
Rotation Speed:	(b) (4) **rpm**
Temperature:	37°C ± 0.5°C
Proposed Specification:	NMT (b) (4) % at 60 minutes
Buffer Stage:	
Apparatus:	II (Paddle)
Medium:	Add 425 mL of buffer concentrate to the remaining 475 mL of solution in each vessel from the Acid Stage to pH 6.8
Volume:	900 mL
Rotation Speed:	(b) (4) **rpm**
Temperature:	37°C ± 0.5°C
Proposed Specification:	NLT (b) (4) % (Q) at (b) (4) minutes after acid stage

(2) In vitro dissolution method procedure and analytical method validation

The detailed analytical procedure for in vitro dissolution (Method # DISLAN03) was submitted in M.3.2.P.5.2.

The dissolution method validation report of drug product (Report# LANS011R) was submitted in M.3.2.P.5.3, Volume D, which were validated in terms of linearity, precision, accuracy, stability, specificity for acid stage; accuracy, linearity, range, precision, repeatability, ruggedness, specificity, system suitability and solution stability for base stage, summarized in Table 3 and 4.

Table 3: Dissolution test DISLAN03 – Validation summary (Report# LANS011R), Acid stage (from M.3.2.P.5.3)

Analytical Parameter	Acceptance Criteria
Linearity	The correlation coefficient square should be not lower than 0.98 for the concentration of 50% - 130% of the specification limit.
Precision and Accuracy	Precision: the coefficient of variation of the test results should be not higher than 3.0% for 6 sample solutions. Accuracy: the mean measured recovery should be 95% to 105% of the theoretical amount for 6 samples with concentrations of (b)(4)% of the specification limit
Solution Stability	The stability of the standard and sample solutions will be tested at room temperature and at 4°C. A change of more than 2% indicates instability of the solutions.
Specificity	The interference should not exceed 2%.

Table 4: Dissolution test DISLAN03 – Validation summary (Report# LANS011R), Buffer stage (from M.3.2.P.5.3)

Analytical Parameter	Acceptance Criteria
Accuracy	The measured recovery should be 95% to 105% of the theoretical amount for 9 samples with concentrations between 50% – 130% of the claimed amount.
Linearity	The correlation coefficient square should be not lower than 0.98 for the concentrations of 50% - 130% of the claimed amount.
Range	The range of the method is between 50% - 130% of the claimed amount.
Precision - Repeatability	The coefficient of variation of the test results should be not higher than 3.0% for 6 sample solutions.
Intermediate Precision (Ruggedness)	The tests will be performed by 3 different analysts using different instruments on the same batch. The difference in mean value should not exceed an absolute of 10% at time points with less than 85% dissolved and should not exceed 5% for time points with more than 85% dissolved.
Specificity	The presence of excipients should not interfere with the analysis.
System suitability	RSD of 5 replicate injections should be no lower than 2.0%.
Solution stability	The stability of standard and sample solutions will be tested at room temperature and at 4°C. A change of more than 2% indicates instability of the solutions.

Reviewer's Assessment:

In M.2.3.P, the Applicant indicated the API (Lansoprazole) is BCS class II (characterized by low solubility and high permeability).

The Biopharmaceutics review team considered the in vitro dissolution method validation is adequate; however, we had one comment regarding the rotation speed changing from recommended 75 rpm to proposed (b)(4) rpm, which was conveyed to the Applicant in the Biopharmaceutics 1st Information Request (IR) as comment #1 below (dated 10/16/2015).

3. The in vitro dissolution data and specifications

In M.2.7.1 Summary of Biopharmaceutics Studies, the Applicant submitted the in vitro dissolution data (N=6 units/batch) of pivotal clinical batch of drug product (Batch No. **BY191113B**) and the listed drug (Prevacid 24 HR 15 mg Lot 120934) using the proposed method (Apparatus II paddle, medium 500 mL 0.1N HCl, after (b) (4) min, add 425 mL buffer to pH 6.8, 100 rpm), see Table 5 and Figure 1:

Table 5: In vitro dissolution data of pivotal clinical batch (Batch No. **BY191113B**) and the listed drug product (Prevacid 24 HR 15 mg Lot 120934) (from M.2.7.1)

Prevacid 24 HR 15 mg Lot 120934									
Time (hr)	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean	SD	RSD (%)
(b) (4)									
BY191113B									
(b) (4)									

Figure 1: Mean Dissolution Profiles of pivotal clinical batch (Batch No. **BY191113B**) and the listed drug product (Prevacid 24 HR 15 mg Lot 120934) (from M.2.7.1)

(b) (4)

Reviewer's Assessment:

Bases on the submitted data, the Biopharmaceutics review team considered that the proposed dissolution specification as: *At acid stage: NMT* (b) (4) *% at 60 minutes; at buffer*

stage: NLT (b) (4)*% (Q) at* (b) (4) *minutes is* (b) (4) for the drug product. Therefore, the following Biopharmaceutics 1st IR was conveyed to the Applicant on 10/16/2015 in FILING REVIEW ISSUES IDENTIFIED letter (74-day letter):

Biopharmaceutics 1st Information Request:

(b) (4)

4. The Responses for the Biopharmaceutics 1st IR:

On 12/04/2015, the Applicant provided responses for the 1st IR above, summarized as:

- Rationale of developing proposed dissolution method;
- Updated the dissolution method, changing from proposed (b) (4) rpm to the USP and FDA recommended 75 rpm rotation speed;
- Additional in vitro dissolution data (N=12 units/batch) of one pivotal clinical batch (Batch No. BY191113B) and two pivotal stability batches (Batch No. BY221113B, and BY011213B) using both dissolution methods (75 rpm and (b) (4) rpm);
- Insisted the original proposed dissolution specification.

The updated in vitro dissolution method was submitted in M.3.2.P.2-addendum-3. The Applicant also updated the related sections as M.2.3.P, M.3.2.P.2, M.3.2.P.5.1, M.3.2.P.5.2, M.3.2.P.5.3 and M.3.2.P.5.6. The updated dissolution method and specification are listed in Table 6:

Table 6: Updated in vitro dissolution parameters and specification for Lansoprazole DR ODT, 15 mg (from 3.2.P.2-addendum-3 of 12/04/2015 submission)

Acid Stage:	
Apparatus:	II (Paddle)
Medium:	0.1 N Hydrochloride Acid (HCl)
Volume:	500 mL
Rotation Speed:	**75 rpm**
Sampling Time:	60 minutes
Temperature:	37°C ± 0.5°C
Proposed Specification:	NMT (b) (4)% at 60 minutes
Buffer Stage:	

Apparatus:	II (Paddle)
Medium:	Add 425 mL of buffer concentrate to the remaining 475 mL of solution in each vessel from the Acid Stage to pH 6.8
Volume:	900 mL
Rotation Speed:	**75 rpm**
Sampling Time:	(b) (4) minutes after acid stage
Temperature:	37°C ± 0.5°C
Proposed Specification:	NLT (b) (4)% (Q) at (b) (4)minutes after acid stage

The additional in vitro dissolution data (N=12 units/batch) of one pivotal clinical batch (Batch No. BY191113B) and two stability batches (Batch No. BY221113B, and BY011213B) using both dissolution methods (75 rpm and (b) (4) rpm) are listed below (Table 7-9 and related figures):

(b) (4)

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

Reviewer's Assessment:

The agreed in vitro dissolution method and specification are summarized as:

Acid Stage:	
Apparatus:	II (Paddle)
Medium:	0.1 N Hydrochloride Acid (HCl)
Volume:	500 mL
Rotation Speed:	75 rpm
Sampling Time:	60 minutes
Temperature:	37°C ± 0.5°C
Specification:	NMT (b)(4)% at 60 minutes
Buffer Stage:	
Apparatus:	II (Paddle)
Medium:	Add 425 mL of buffer concentrate to the remaining 475 mL of solution in each vessel from the Acid Stage to pH 6.8
Volume:	900 mL
Rotation Speed:	75 rpm
Sampling Time:	(b)(4) minutes after acid stage
Temperature:	37°C ± 0.5°C
Interim Specification in Advice Letter dated 02/09/2016:	NLT (b)(4)% (Q) at 45 minutes after acid stage
Recommended Specification in Biopharm 2nd IR dated on 12/23/2015:	*NLT (b)(4)% (Q) at (b)(4) minutes after acid stage*

7. In vitro alcohol dose dumping study

In original NDA submission (12/05/2014), an in vitro alcohol-induced dose dumping study was conducted using 0.1N HCl with 5%, 20% and 40% (v/v) of Alcohol (App. 2 paddles; 100 rpm). Drug release data of proposed drug and the listed drug were collected every 15 minutes for a total of 1 hour, given in Table 17 (from M.3.2.P.2).

Table 17: Alcohol-induced dose dumping study in original NDA submission (from M.3.2.P.2)

Drug release		Lansoprazole DR ODT, 15 mg	Prevacid 24 HR capsules
Medium	Time (min)	B.N BY011213B	Lot 120934
HCl 0.1 N + 5% Alcohol	15	2%	4%
	30	3%	5%
	45	4%	5%
	60	5%	5%
HCl 0.1 N + 20% Alcohol	15	1%	1%
	30	3%	2%
	45	5%	3%
	60	13%	8%
HCl 0.1 N + 40% Alcohol	15	19%	94%
	30	63%	107%
	45	96%	111%*
	60	104%	114%*

In this NDA resubmission (08/05/2015), the in vitro alcohol-induced dose dumping study was repeated on the final drug product (Pivotal clinical batch, BY191113B) and the listed drug (Prevacid 24 HR 15 mg Lot 120934) and submitted in M.2.7.1. The method of analysis was based on the finished product validated method (DISLAN03) for acid stage using apparatus 2 (paddles) at 100 rpm, followed by UV spectrophotometer determination. The following method was described as [from M.2.7.1. *Note: on 03/18/2016, the Applicant responded the Biopharmaceutics IR issued on 03/17/2016, and corrected the typos of HCl 0.1N solutions calculation in the in vitro alcohol dose dumping study (page 27/31)*]:

- *Different levels of alcohol were added to the dissolution medium*
  - *0% (500 mL HCl 0.1N)*
  - *5% (25 mL ethanol, 475 mL HCl 0.1N)*
  - *10% (50 mL ethanol, 450 mL HCl 0.1N)*
  - *20% (100 mL ethanol, 400 mL HCl 0.1N)*
  - *40% (200 mL ethanol, 300 mL HCl 0.1N)*
- *Collection of samples was immediately followed by dilution by 0.5M NaOH in a ratio of (1:1) (v/v) for maintaining the solutions stability.*

Drug release data of proposed drug and the listed drug were collected every 15 minutes for a total of 1 hour, given in Table 18 (from M.2.7.1).

Table 18: Alcohol-induced dose dumping study in NDA resubmission (from M.2.7.1)

Drug Release		Lansoprazole Delayed Release ODT, 15 mg (BY191113B) Average of 12 tablets	Prevacid 24 HR capsules Lot 120934 Average of 12 tablets
Medium	Time (min)		
HCl 0.1N + 0% Alcohol	15	1%	
	30	1%	
	45	1%	
	60	1%	
HCl 0.1N + 5% Alcohol	15	1%	
	30	1%	
	45	2%	
	60	2%	
HCl 0.1N + 10% Alcohol	15	1%	
	30	2%	
	45	2%	
	60	4%	
HCl 0.1N + 20% Alcohol	15	< 0.25% (QL)	
	30	<0.25% (QL)	
	45	2%	
	60	10%	
HCl 0.1N + 40% Alcohol	15	10.2%	83.6%
	30	74.0%	120.8%
	45	97.5%	124.8%
	60	101.9%	121.6%

The Applicant indicated that "*the compressed tablets demonstrated similar dissolution behavior in comparison to the control (0% alcohol) and the dissolution specification of*

10% drug release in the acid medium under all tested alcohol concentrations with the exception of the 40% alcohol medium, in which the Prevacid 24 HR product was also compromised. The in vitro alcohol dose dumping study demonstrated premature release of lansoprazole with alcohol at concentrations of ≥ 40%, ie, a shot of alcohol, but not a glass of wine or beer. These results indicate that in cases of higher alcohol concentrations the (b) (4) *coating is compromised so the in vivo result will be premature release of drug in the stomach. Since lansoprazole is an acid-labile drug, an exposure of the drug to this gastric acid will lead to degradation of lansoprazole and result in ineffective drug. No greater drug exposure due to the compromised* (b) (4) *coat is expected*".

Reviewer's Assessment:

There is in vitro alcohol dose dumping effect of proposed drug product, Lansoprazole DR ODT, 15 mg, observed. The in vitro results had been communicated to the Office of Clinical Pharmacology (OCP). Therefore, the Waiver request of In Vivo Alcohol-Induced Dose Dumping Testing (in M.1.12.15) needs to be addressed by OCP.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

From Biopharmaceutics perspective:

- The proposed in vitro dissolution method for the drug product, Lansoprazole Delayed-Release Orally Disintegrating Tablets (DR ODT), 15 mg, is acceptable;
- The in vitro dissolution method validation for the proposed drug product is well established and acceptable;
- The proposed drug product showed in vitro alcohol dose dumping effect when using 40% alcohol ;
- The Applicant accepted the Agency's recommendations about the interim dissolution specification. They will collect/generate dissolution data on 12 tablets per batch for every batch released to the market post-approval both in the acid stage and especially at (b) (4) 45 min in the buffer stage, and the complete dissolution profile data will be submitted in the first Annual Report. If the data support a change in specification, the sponsor will submit the new specification in a CBE. If the data do not support the change in the specification, the sponsor will contact the agency and provide justification with data for the Agency to review and discussion.
- The agreed in vitro dissolution method and interim specification for the proposed drug product one year post approval are summarized as below:

Acid Stage:	
Apparatus:	II (Paddle)
Medium:	0.1 N Hydrochloride Acid (HCl)
Volume:	500 mL
Rotation Speed:	75 rpm
Sampling Time:	60 minutes
Temperature:	37°C ± 0.5°C
Specification:	NMT (b)(4)% at 60 minutes
Buffer Stage:	
Apparatus:	II (Paddle)
Medium:	Add 425 mL of buffer concentrate to the remaining 475 mL of solution in each vessel from the Acid Stage to pH 6.8
Volume:	900 mL
Rotation Speed:	75 rpm
Sampling Time:	(b)(4) minutes after acid stage
Temperature:	37°C ± 0.5°C
Interim Specification:	NLT (b)(4)% (Q) at 45 minutes after acid stage

OVERALL COMMENTS:

This NDA 208025 for drug product, Lansoprazole Delayed-Release Orally Disintegrating Tablets (DR ODT), 15 mg, is reviewed and found acceptable from the Biopharmaceutics perspective; therefore, this NDA 208025 is recommended for APPROVAL.

03/23/2016
Mei Ou, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Products

Mei Ou -S
Digitally signed by Mei Ou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mei Ou -S, 0.9.2342.19200300.100.1.1=2001622313
Date: 2016.03.24 10:33:39 -04'00'

Secondary Review Comments and Concurrence:

I concur 03/23/16

Tien-Mien Chen, Ph.D.
Acting Biopharmaceutics Lead
Office of New Drug Products

Tienmien Chen -S
Digitally signed by Tienmien Chen -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tienmien Chen -S, 0.9.2342.19200300.100.1.1=1300073135
Date: 2016.03.24 10:37:39 -04'00'

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

OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment and Signature: Adequate. Pei-I Chu Peii Chu -S

Secondary Review Comments and Concurrence:

Concur with reviewer's assessment and conclusion, Ubrani V, Venkataram,

Ubrani V. Venkataram -S

ASSESSMENT OF MICROBIOLOGY

10. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: No microbial limit tests were proposed

Reviewer's Assessment: Not Adequate. Refer to question 34.

However, see review on pages 70 and 71 and also conclusion below on page 76

2.3.P.7 Container/Closure System

11. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: N.A.

Reviewer's Assessment: This is an oral product. The container closures selected are commonly used by the pharmaceutical industry for oral product. It is not necessary to demonstrate this container closure to be a barrier to microbial ingress since this is not a parenteral dosage form.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

12. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: There are no excipients of human or animal origin in Lansoprazole Delayed-Release Orally Disintegrating Tablets, 15 mg.

Reviewer's Assessment: Adequate. The applicant provided statements that no excipients are derived from human or animal origin.

13. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: N.A.

Reviewer's Assessment: N.A.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Adequate. Peii Chu -S

Secondary Review Comments and Concurrence:

Concur with reviewer's assessment and conclusion of microbiology, Ubrani V.Venkataram, Ubrani V. Venkataram -S

NDA 208025
Review # 1

Drug Name/Dosage Form	Lansoprazole Orally disintegrating tablets
Strength	15 mg
Route of Administration	Oral
Rx / OTC Dispensed	OTC
Applicant	Dexcel Pharma Technologies Ltd. 1 Dexcel St., Or-Akiva, Israel 3060000 C/O Camargo Pharmaceutical Services LLC 9825 Kenwood Road, STE 203 Cincinnati, OH 45242
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	08-Jul-2015	ONDP/OPF/FR
Amendment	11-Nov-2015	ONDP
Amendment	10-Mar-2015	ONDP
Amendment	11-Jan-2016	OPF/ONDP
Amendment	10-Mar-2016	OPF

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Erin Skoda, Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Muthukumar Ramaswamy, Ph.D.	ONDP/DNDP-II/ Branch VI
Process	Pei-I Chu, Ph.D.	OPF/DPAII/BranchVI
Microbiology	Pei-I Chu, Ph.D.	OPF/DPAII/BranchVI
Facility	Juandria Williams, Ph.D.	OPF/DIA/B3
Biopharmaceutics	Mei Ou, 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)	Muthukumar Ramaswamy, 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 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.
	Type III			Adequate	N/A	Sufficient data in the application.
	Type IV			Adequate	N/A	Sufficient data in the application.
	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)

[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-208025)

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;

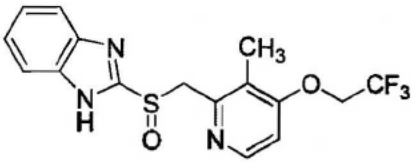
Drug substance (Lansoprazole) information is referred to a Type II DMF (b) (4). The current status of the DMF is adequate and last reviewed on 04/13/2012. Some basic information is shown below.

1. Drug Substance [USAN Name] Quality Summary

Name (USAN) : Lansoprazole

Chemical Name (IUPAC): 2-[[[3-methyl-4-(2,2,2-trifluorethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazole
2-(2-Benzimidaolylsulfinylmethyl)-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine
2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]-methyl]sulfinyl]benzimidazole

Code Name: n/a
CAS number: 103577-45-3



Lansoprazole is a white to off-white (b) (4) powder that is practically insoluble in water, slightly soluble in acetonitrile, soluble in methanol and freely soluble in DMF.

(b) (4)

A. Drug Product [Lansoprazole] Quality Summary

1. Strength: 15 mg

2. Description/Commercial Image:

Lansoprazole 15 mg delayed release orally disintegrating tablet for over-the-counter (OTC) use is indicated for the treatment of heartburn (15 day use). NDA 208025, a 505(b)2 application is relying on the safety and efficacy information from Prevacid® 24 hour delayed release capsule (NDA 22327), which relies on non-clinical information available for Prevacid® capsules (NDA 20406). The tablet is white to off white mottled (with white to off -white to grayish to pinkish pellets) uncoated tablet; embossed "15" on one side. The theoretical tablet weight is approximately 250 mg based on a yield corresponding to 100%.

3. Summary of Product Design

This proposed dosage form is an orally disintegrating tablet containing 15 mg of lansoprazole. Lansoprazole is provided as (b) (4) 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.

The proposed drug product is manufactured (b) (4)

4. List of Excipients:

(b) (4), mannitol, hypromellose (b) (4) talc, titanium dioxide, crospovidone, colloidal silicon dioxide, meglumine, polysorbate 80, hypromellose

phthalate (b) (4) cetyl alcohol, triethyl citrate, (b) (4) sucralose, ascorbic acid, sodium stearyl fumarate, (b) (4) and Strawberry flavor.

(b) (4)

[redacted]

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 12-month study at long-term storage conditions (25°C/60% RH) and 6-month study at accelerated conditions (40°C/75% RH).
The storage statement will be written as "Store at 20°C – 25°C (68°F - 77°F); keep out of high heat and humidity; protect from 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	Lansoprazole
Non Proprietary Name of the Drug Substance	Lansoprazole
Proposed Indication(s) including Intended Patient Population	Treats frequent heartburn (occurs 2 or more days a week)
Duration of Treatment	One tablet a day; 14-Day course of Treatment; May repeat a 14-Day Courses every 4 months; Adults 18years of age and older.
Maximum Daily Dose	15 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# 120383 and study# 120384) 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. OPQ has identified following item for discussion.

a) Container label is missing critical information for bar code, NDA number, storage information and lot number.
b) "Keep out of reach of children" statement is missing in the carton label.

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	Similar assay method as approved for capsule dosage form. Impurities are monitored.
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Stable based on limited data provided.

Content uniformity	• Formulation • Raw materials • Process parameters •Scale/equipment • Site	3	2	2	12	(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	Interim specification will be used and data will be generated and submitted in the first annual report.

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: 2016.04.22 11:28:28 -04'00'

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

QUALITY ASSESSMENT

Reviewer's Assessment and Signature: Adequate
NDA 208025 contains adequate CMC information on the proposed drug product. Based available stability information, CMC reviewer is granting 24 month shelf-life for the storage of the product in HDPE bottles or blister packs at 25°C/60% RH.

4/18/16
Muthukumar Ramaswamy
Office of New Products

Muthukumar Ramaswamy -S
Digitally signed by Muthukumar Ramaswamy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000341660, cn=Muthukumar Ramaswamy -S
Date: 2016.04.18 16:43:47 -04'00'

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.

Danae D. Christodoulou -S
Digitally signed by Danae D. Christodoulou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -S
Date: 2016.04.20 14:16:49 -04'00'

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

11. Is the applicant's claim for categorical exclusion acceptable?

12. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response: Dexel Pharma is seeking exemption from the requirement for preparing and submitting an Environmental Assessment to 2 1 CFR §25.15 (d) and 21 CFR §25.20 (1) for the following reasons:

a) Per 21 CFR §25.31 (a), an exemption from preparing EA is permitted if the action on NDA does not increase the use of the active moiety. Dexcel 's Lansoprazole Delayed Release Orally Disintegrating Tablets 15 mg will be administered at the same dosage level, for the same duration and for the same indication as the listed drug, Prevacid® 24 HR, 15 mg capsules.
b) Once approved, use of Dexcel's product would in all likelihood displace the use of the currently marketed product, and thus would not increase the use of the active moiety in the environment.

Reviewer's Assessment: Adequate

Dexel Pharma requests to exempt from preparing and submitting an Environmental Assessment is granted for the following reasons:

a) Lansoprazole (Prevacid® 24 HR, 15 mg capsules) is an approved drug. Dexel's drug is the same strength as the approved drug. NDA approval action will not increase the use of the active moiety.

b) Once approved, use of Dexcel's product would not increase the use of the active moiety in the environment as the product would be competing with the same market targeted by the approved drug.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: Adequate

Dexel Pharma's request to exempt from preparing and submitting an Environmental Assessment for Lansoprazole delayed release ODT is granted.

Muthukumar Ramaswamy -S

Digitally signed by Muthukumar Ramaswamy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000341660, cn=Muthukumar Ramaswamy -S
Date: 2016.04.18 16:44:21 -04'00'

Secondary Review Comments and Concurrence:

I concur with the reviewer's assessment.

Danae D. Christodoulou -S

Digitally signed by Danae D. Christodoulou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -S
Date: 2016.04.20 14:17:43 -04'00'

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert - OTC Product

Established name, strength, dosage form, route of administration appear in the package insert correctly.

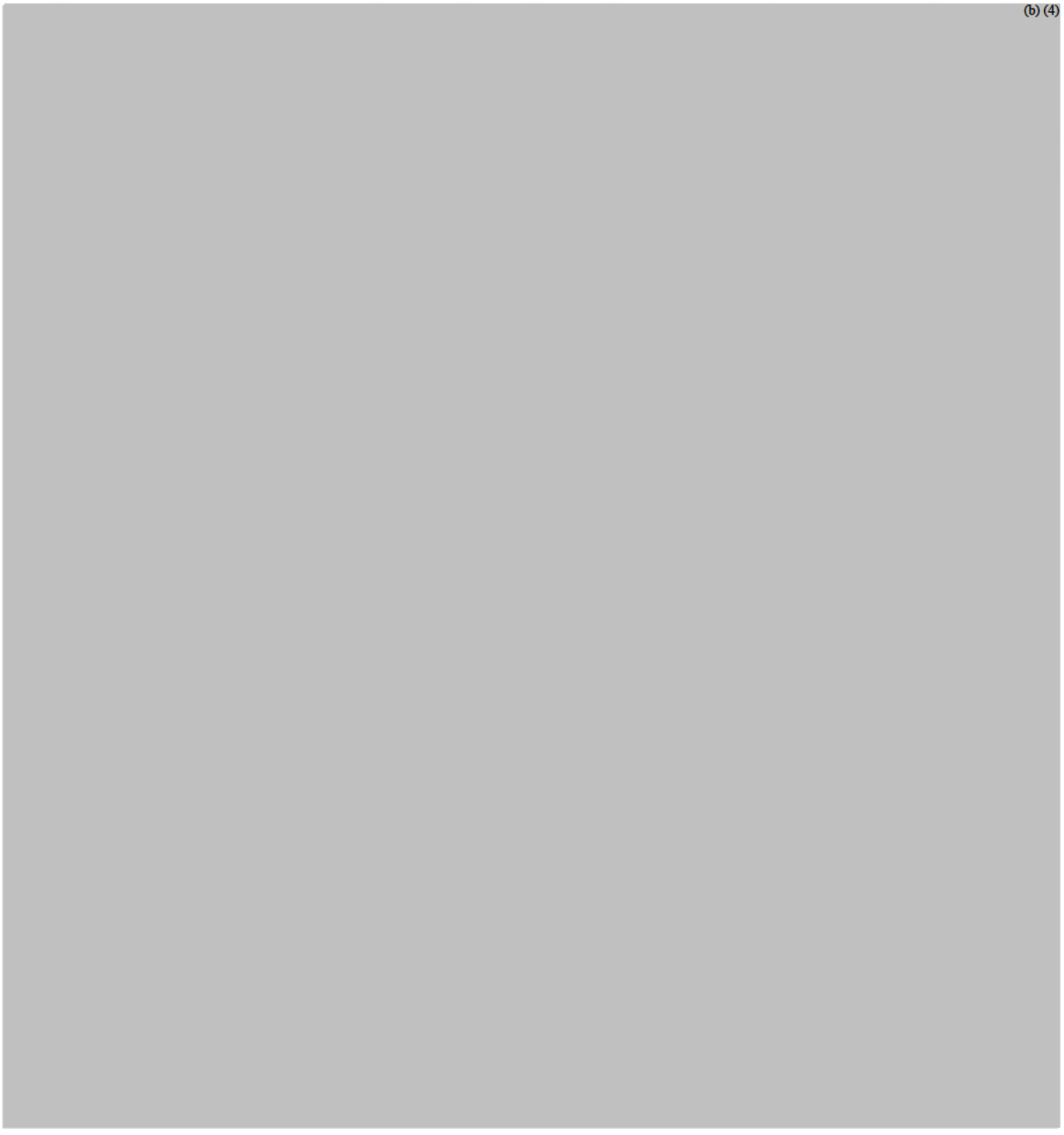
OTC product - Proprietary name not provided.

(a) "Highlights" Section (21CFR 201.57(a)) - Not Applicable
(b) "Full Prescribing Information" Section - Not Applicable
3: Dosage Forms and Strengths (21CFR 201.57(c)(4))
#11: Description (21CFR 201.57(c)(12))
#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

2. Container and Carton Labeling

Representative label for a 14ct Blister Pack configuration is shown below.

(b) (4)



QUALITY ASSESSMENT

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Not available Lansoprazole	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	15 mg	Adequate
Route of administration 21.CFR 201.100(b)(3))	Oral	Adequate
Net contents* (21 CFR 201.51(a))	14 tablets, 28 tablets, 42 tablets	Adequate
Name of all inactive ingredients (Quantitative ingredient information is required for injectable) 21CFR 201.100(b)(5)**	Not specified in both blister and bottle label	Not specified
Lot number per 21 CFR 201.18	Yes. Available for bottle label Not available for blister label	Not specified
Expiration date per 21 CFR 201.17		
"Rx only" statement per 21 CFR 201.100(b)(1)	Not applicable in both blister and bottle label	Not applicable
Storage (not required)	Yes. Available for bottle label Not available for blister label	Not required
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Not available for both label	Missing information
Bar Code per 21 CFR 201.25(c)(2)***	Not available for both label	
Name of manufacturer/distributor (21 CFR 201.1)	Available for both label	
Others		

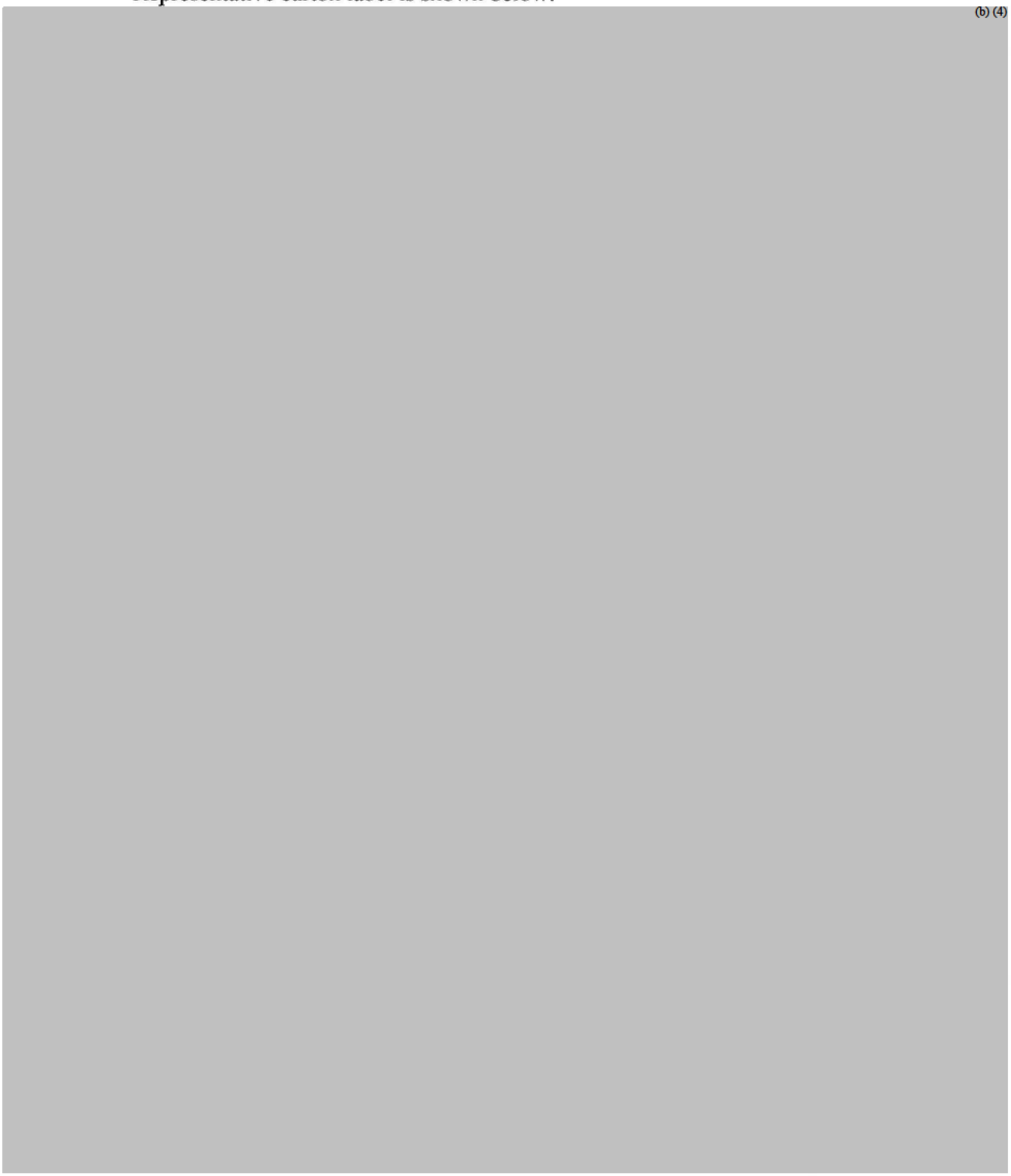
*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate with comment.
Labeling review will be completed during OND labeling review. Preliminary assessment indicates that bar code, NDC number, storage info, lot # is missing.

1) Carton Labeling

Representative carton label is shown below.

(b) (4)



QUALITY ASSESSMENT

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Not available Lansoprazole	Proprietary name not available
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	15 mg	
Net contents (21 CFR 201.51(a))	14 tablets, 28 tablets, 42 tablets	
Lot number per 21 CFR 201.18	Yes	
Expiration date per 21 CFR 201.17	Yes	
Name of all inactive ingrédients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Ascorbic Acid, cetyl alcohol, colloidal silicon dioxide, copovidone, crospovidone, flavor, hypromellose, hypromellose phthalate, maize maltodextrin, maltitol, mannitol, meglumine, microcrystalline cellulose, polysorbate 80, propylene glycol, silicon dioxide, Sodium Stearyl Fumarate, sorbitol, Sucralose, (b) (4) talc, titanium dioxide, triethyl Citrate.	Acceptable
Sterility Information (if applicable)	Not applicable	
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Not available	
Storage Conditions	Yes. Information accurate	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Available	
Bar Code per 21 CFR 201.25(c)(2)**	Yes	
Name of manufacturer/distributor	Yes	
"See package insert for dosage information" (21 CFR 201.55)	Not indicated in the label	Not applicable
"Keep out of reach of children" (optional for Rx, required for OTC)	Not indicated in the label	**Missing**
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		

Conclusion: Adequate with comment

Labeling review will be performed as a team review.

Keep out of reach of children statement is missing from the carton label.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Adequate
Please note labeling review will be completed as a team review with OND review team. Missing information will be communicated during that time.

Muthukumar Ramaswamy -S
Digitally signed by Muthukumar Ramaswamy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000341660, cn=Muthukumar Ramaswamy -S
Date: 2016.04.18 16:45:48 -04'00'

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.

Danae D. Christodoulou -S
Digitally signed by Danae D. Christodoulou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -S
Date: 2016.04.20 14:18:43 -04'00'

II. List of Deficiencies To Be Communicated during labeling:

Drug Product

Label/Labeling
Label conformance to OTC product label requirements will be completed during labeling review with OND. However preliminary assessment per OPQ review template indicated the following:

a) Container label is missing the following information: Bar code, NDC number, storage info, and lot #.
b) Keep out of reach of children statement is missing from the carton label.

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