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RESEARCH**

APPLICATION NUMBER:

218527Orig1s000

PRODUCT QUALITY REVIEW(S)



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Template Revision: 03

Office of Pharmaceutical Quality

New Drug Application (NDA) Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	NDA 218527
Applicant Name	B Better, LLC
Drug Product Name	Tadalafil Chewable Tablets
Dosage Form	Tablet, chewable
Proposed Strength(s)	5 mg, 10 mg, 20 mg
NDA Classification	Type 3 - New Dosage Form
Route of Administration	Oral
Maximum Daily Dose	20 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of erectile dysfunction and benign prostatic hyperplasia.
Drug Product Description	B Better, LLC, has submitted this 505(b)(2) application for Tadalafil Chewable Tablets, 5 mg, 10 mg, 20 mg indicated to the treatment of erectile dysfunction and benign prostatic hyperplasia. The drug substance, tadalafil is a phosphodiesterase 5 (PDE5) inhibitor and was first approved on November 21, 2003 as the active ingredient of Cialis under NDA 021368. Since its original approval multiple brand name and generic drug products containing this active ingredient have been approved for marketing in the United States. Tadalafil Chewable tablets are round-shaped, blue colored (mottled), biconvex uncoated tablets for oral administration. Each tablet contains 5 mg or 10 mg of tadalafil as the active ingredient, and bubblegum flavor (acacia, artificial and natural flavors), colloidal silicon dioxide, croscarmellose sodium, FD&C blue No. 1 aluminum lake, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, mannitol,

	microcrystalline cellulose, sodium lauryl sulfate, and sucralose as inactive ingredients. 5 mg, 10 mg, and 20 mg tadalafil chewable tablets are debossed on one side with “N627”, “N628”, and “N629”, respectively and plain on the other side. 5 mg strength is packaged in HDPE bottles as 1000-count tablets, 10 mg strength is packaged in HDPE bottles as 750-count tablets, and 20 mg strength is packaged in HDPE bottles as 500-count tablets. Bottles are closed with (b) (4) caps integrated with 1-g silica gel desiccant. Tadalafil chewable tablets should be stored at 20°C – 25°C (68°F – 77°F); excursion permitted from 15°C – 30°C (59°F – 86°F) [See USP Controlled Room Temperature]. An expiration dating period of 24 months is currently granted to this drug product.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	Store at 20°C – 25°C (68°F – 77°F); excursion permitted from 15°C – 30°C (59°F – 86°F) [See USP Controlled Room Temperature]		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Sukhamaya Bain, Ph.D.	Lawrence Perez, Ph.D.
	<i>Drug Product/ Labeling</i>	Ghaled Hamad, Ph.D.	Hamid Shafiei, Ph.D./Julia Pinto, Ph.D.
	<i>Manufacturing</i>	Mesfin Abdi, Ph.D.	Jean Tang, Ph.D.
	<i>Biopharmaceutics</i>	Rajesh Savkur, Ph.D.	Tapash Ghosh, Ph.D.
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify Environmental Assessment (categorical Exclusion))</i>	Ghaled Hamad, Ph.D.	Hamid Shafiei, Ph.D.

	<i>RBPM</i>	Stephanie Ngan
	<i>ATL</i>	Hamid Shafiei, Ph.D.
Consults	N/A	

2. Final Overall Recommendation - Approval

This application is recommended for approval from all OPQ review disciplines, and the final agreed labeling and container closure labels that have been communicated through the clinical team to the applicant and have been accepted. The revised labeling and container closure labels that reflect the recommended changes will be submitted to this application prior to PDUFA action date. Based on the acceptance by the applicant of recommended labeling/labels changes, the labeling review is now considered adequate although in the original labeling review chapter the container closure was found as inadequate. Therefore, no additional labeling memorandum will be attached to the labeling review chapter.

During the application review, the applicant submitted requests for trade names. However, all trade name requests by the applicant were denied by the Agency. Therefore, this application will be approved without the drug product trade name as Tadalafil Chewable Tablets.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, tadalafil and the drug product, Tadalafil Chewable Tablets, 5 mg, 10 mg, and 20 mg.
- The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC recommended changes to the labeling have been communicated to the Clinical Review Team and the proposed CMC revisions have been accepted.
- The applicant's request for categorical exclusion from the preparation of environmental assessment has been found adequate and is granted.

Therefore, this applicant is recommended for approval from the OPQ perspective with an expiration dating period of 24 months.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate
Biopharmaceutics	-	Adequate
Microbiology	-	N/A

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Yes

5. Life-Cycle Considerations
Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Application Technical Lead Name:

Hamid Shafiei, Ph.D.
Senior Pharmaceutical Quality Assessor
DPQA VII/OPQA II/OPQ



Hamid
Shafiei

Digitally signed by Hamid Shafiei

Date: 5/12/2024 09:16:35PM

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Title:	NDA IQA Template CHAPTER IV- LABELING		
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Template Revision: 03

CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide \(OPQ-ALL-WI-0006\)](#)

NDA Number	218527
Assessment Cycle Number	1
Drug Product Name	Tadalafil Chewable Tablets, 5 mg, 10 mg, and 20 mg

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	5
Patient Information	Adequate	
Instruction for Use (IFU)	Adequate	
Container Labels	Inadequate	
Carton Labeling	N/A	

Brief Description of Outstanding Issues:

- The container label for tadalafil chewable tablets states "(b) (4)" which creates confusion (b) (4). The prescribing information (PI) also lacks guidance on splitting, potentially leading to misinterpretation. To address this inconsistency and improve clarity for patients, we propose the following revisions:
 - Remove the phrase (b) (4) from the container label.
 - Add a clear statement to the PI and throughout the labeling explaining that the tablets are not scored and should not be split or broken.
 - Keep the existing instruction to chew tablets completely before swallowing and remove (b) (4) from the container label and throughout the labeling.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0001, 5	10/12/2023	Draft Labeling

1.0 PRESCRIBING INFORMATION¹

Assessment of Product Quality Related Aspects of the Prescribing Information:

Submitted on November 29, 2023, SDN 0003 and October 12, 2023, SDN 0002



1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights² [21 CFR 201.57(a)(2)]		
Established name(s) ³	Adequate	
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s) ⁴ and strength(s) in metric system ⁵	Adequate	

¹ [Labeling Review Tool \(LRT\) \(March 2022\)](#), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

² Draft guidance: [Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format](#) (January 2018)

³ Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

⁴ Draft guidance: [Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format](#) (January 2018); USP <1151>; USP Nomenclature Guideline

⁵ [Labeling Review Tool \(March 2022, page 13\)](#), include limited packaging information; USP <7>

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). ⁶	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." ⁷	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. ⁸	N/A	

Assessment: *Adequate*

⁶ Guidance: [Naming of Drug Products Containing Salt Drug Substances](#) (June 2015); MAPP 5021.1

⁷ Guidance: [Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation](#) (March 2013)

⁸ Guidance: [Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use](#) (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)⁹

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food ¹⁰ , storage conditions needed to maintain the stability of the reconstituted or diluted product).	Adequate	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	
For parenteral products: include statement: <i>"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i> ¹¹	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. ¹² Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the	N/A	

⁹ See § 201.57(c)(3); draft guidance: [Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format](#) (January 2023); Labeling Review Tool (March 2022, page 25)

¹⁰ Draft Guidance: [Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments](#)

¹¹ §201.57(c)(3)(iv)

¹² USP General Notices 2.30 Legal Recognition

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
patient and healthcare practitioner(s) who administer the drug		
For hazardous products, include the statement <i>"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x"</i> with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)¹³

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and	Adequate	

¹³ See § 201.57(c)(4); [Labeling Review Tool \(March 2022, page 29\)](#)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
color and clarity of the solution, when applicable.		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: *Adequate*

1.2.3 Section 11 (DESCRIPTION)¹⁴

(b) (4)

¹⁴ See § 201.57(c)(12); [Labeling Review Tool \(March 2022, page 56\)](#)

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s) ¹⁵ [§ 201.57(c)(12)(i)(A)].	Adequate	
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	N/A	
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order. ¹⁶ Avoid	Adequate	Bubblegum flavor (acacia, artificial and natural flavors), colloidal silicon dioxide, croscarmellose sodium, FD&C blue No. 1 aluminum lake,

¹⁵ Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

¹⁶ Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients,

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
brand names. [§ 201.57(c)(12)(i)(C)].		hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, sodium lauryl sulfate and sucralose.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class ¹⁷ [§ 201.57(c)(12)(i)(E)].	Adequate	
Chemical name ¹⁸ , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	N/A	
For oral prescription drug products, include gluten statement ¹⁹ (if applicable).	N/A	

recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

¹⁷ Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in [FDA's Labeling Resources for Human Prescription Drugs](#) for the most recent EPC list.

¹⁸ Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

¹⁹ Draft guidance: [Gluten in Drug Products and Associated Labeling Recommendations \(December 2017\)](#)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Adequate*

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)²⁰

(b) (4)

²⁰ See § 201.57(c)(17); [Labeling Review Tool \(March 2022, page 70\)](#). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	NDC 70954-627-10. NDC 70954-628-10. NDC 70954-629-10.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^x " with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: " <i>Not made with natural rubber latex. Avoid statements such as "latex-free."</i> " ²¹	N/A	
Include information about child-resistant packaging ²² (if chosen by manufacturer).	Adequate	

Assessment: Adequate

²¹ Guidance: [Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex](#) (December 2014)

²² Guidance: [Child-Resistant Packaging Statements in Drug Product Labeling](#) (August 2019)

1.2.5 Other Sections of Labeling

N/A.

1.2.6 Manufacturing Information After Section 17 (for drug products)²³

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²⁴	Adequate	
Special preparation instructions (if applicable).	Adequate	
Storage and handling information (if applicable).	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	Adequate	
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Adequate	

²³ § 201.1(h)(5) and 201.1(i); [Labeling Review Tool \(March 2022, page 74\)](#)

²⁴ Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

3.2 Carton Labeling

N/A; the carton label was not included in the NDA-218527 submission by the applicant. The drug product is supplied to the pharmacy store in large bottles, with stock sizes outlined in the original NDA submission as 500, 750, and 1000 count presentations. Consequently, there is no need for a carton label for this specific drug product.

Item	Item in Proposed Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name ²⁷ , (font size and prominence) [§ 201.10(g)(2)].	Inadequate	Choose an item.	The proprietary name, (b) (4) was found unacceptable by DMEPA on November 22, 2023. This decision was communicated to the Applicant on November 27, 2023.
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)]. ²⁸	Adequate	Choose an item.	

²⁷ Established name = [Drug] [Route of Administration] [Dosage Form]

²⁸ Express as "XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: [Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors \(May 2022\)](#)

Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Choose an item.	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Adequate	Choose an item.	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)]. ²⁹	Adequate	Choose an item.	
“Rx only” displayed on the principal display [§ 201.100(b)(1)].	Adequate	Choose an item.	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Choose an item.	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Choose an item.	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Choose an item.	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement. (See USP <659>).	N/A	Choose an item.	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	Choose an item.	

²⁹ § 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 parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Choose an item.	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Choose an item.	
Linear Bar code [§ 201.25(c)(2)]. ³⁰	Adequate	Choose an item.	
Adequate directions for use: “Recommended Dosage: See Prescribing Information” [§ 201.5 & 201.55].	Adequate	Choose an item.	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Choose an item.	
“Keep out of reach of children” statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Choose an item.	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Choose an item.	
No text on Ferrule and Cap over seal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Choose an item.	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Choose an item.	

³⁰ See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. ³¹	N/A	Choose an item.	
And others if space is available.	N/A	Choose an item.	

Assessment of Carton Labels and Container Labeling: Adequate

The carton label was not included in the NDA-218527 submission by the applicant.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

- The container label for tadalafil chewable tablets states "(b) (4)" which creates confusion (b) (4) The prescribing information (PI) also lacks guidance on splitting, potentially leading to misinterpretation. To address this inconsistency and improve clarity for patients, we propose the following revisions:
 - Remove the phrase "(b) (4)" from the container label.
 - Add a clear statement to the PI and throughout the labeling explaining that the tablets are not scored and should not be split or broken.
 - Keep the existing instruction to chew tablets completely before swallowing and remove (b) (4) from the container label and throughout the labeling.

Primary Drug Product Assessor Name and Date:

Ghaled Hamad, Ph.D.

Drug Product Reviewer

OPQ/OPQA II/ Division VII/Unit 1

Secondary Assessor Name and Date:

Julia Pinto, Ph.D.

Supervisory chemist

³¹ USP General Notices 3.20 Indicating Conformance

OPQ/OPQA III/ DPQAVIII



Julia
Pinto

Digitally signed by Julia Pinto

Date: 4/17/2024 03:34:19PM

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Ghaled
Hamad

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Date: 4/18/2024 09:36:26AM

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-218527-ORIG-1
Submission History	8/30/2023 (Sequence 0001): Original submission
Drug Product Name/ Strength	(b) (4) – Tadalafil Chewable Tablets, 5 mg, 10 mg and 20 mg
Route of Administration	Oral
Applicant Name	B Better LLC
Therapeutic Classification/ OND Division	Division of Urology, Obstetrics and Gynecology (DUOG)
Proposed Indication	Tadalafil chewable tablets, a selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5), is indicated for the treatment of (i) erectile dysfunction (ED), for use as needed prior to sexual activity; (ii) signs and symptoms of benign prostatic hyperplasia (BPH), taken at approximately the same time every day; and (iii) coexisting ED and BPH, taken at approximately the same time every day.
IND Number	IND-162564
Primary Reviewer	Rajesh Savkur, Ph.D.
SPQA	Tapash Ghosh, Ph.D.
Assessment Recommendation	Adequate

EXECUTIVE SUMMARY

In this submission, the Applicant seeks approval of (b) (4) – Tadalafil Chewable Tablets, 5 mg, 10 mg and 20 mg. Tadalafil chewable tablets, a selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5), is indicated for the treatment of (i) erectile dysfunction (ED), for use as needed prior to sexual activity; (ii) signs and symptoms of benign prostatic hyperplasia (BPH), taken at approximately the same time every day; and (iii) coexisting ED and BPH, taken at approximately the same time every day. NDA-218527-ORIG-1 was initially submitted to the Division of Urology, Obstetrics, and Gynecology on 8/30/2023 under section 505(b)(2). The proposed product relies in part on the FDA's prior determination of safety and effectiveness of the Listed Drug (LD), Cialis (Tadalafil) Tablets, 2.5 mg, 5 mg, 10 mg and 20 mg, (NDA-021368; 5 mg, 10 mg and 20 mg strengths approved on 11/21/2003; 2.5 mg approved on 1/7/2008) developed by Eli Lilly and Co. The current submission seeks approval of the 5 mg, 10 mg and 20 mg strengths. The recommended starting dose of (b) (4) for:

- ED is 10 mg as needed prior to sexual activity, that can be increased to 20 mg or decreased to 5 mg based upon efficacy/tolerability.
- BPH is 5 mg, taken at approximately the same time every day.
- ED and BPH: 5 mg, taken at approximately the same time every day.

The product may be taken without regard to food, and with or without the aid of water.

Due to the lack of the 2.5 mg dose in the current submission, the proposed product is not approved for:

- Once daily use for ED.
- Once daily use for patients using CYP3A4 inhibitors (e.g., ketoconazole, ritonavir).
- ED/BPH in patients with creatinine clearance less than 50 mL/min.

Assessment Summary:

The Biopharmaceutics assessment focuses on evaluating (i) the *in vitro* dissolution method development, the dissolution data and the dissolution acceptance criterion, (ii) the bridging data between the clinical and commercial/to-be-marketed drug products, the manufacturing sites, batch sizes, and (iii) waiver of bioequivalence for the 5 mg and 10 mg strengths.

• **In Vitro Dissolution Method and Acceptance Criterion:**

The proposed drug product is an immediate release product wherein the tadalafil API is a low-solubility drug substance. The dissolution method proposed by the Applicant for Quality Control (QC) of the drug product demonstrates discriminating ability towards a variant batch that differs in the concentration of (b) (4) and a variant batch that is not bioequivalent to the Listed Drug (LD) product. The proposed dissolution acceptance criterion is supported by the dissolution data of the exhibit/clinical batches, and possesses the ability to reject the variant and non-bioequivalent batches. Based on the information submitted, the following dissolution method and acceptance criterion as shown below in Table 1 are agreed for the QC test of Tadalafil chewable tablets, 5 mg, 10 mg and 20 mg, at batch release and through stability.

Table 1: Approved dissolution method and acceptance criterion for Tadalafil chewable tablets, 5 mg, 10 mg and 20 mg

Approved dissolution method				Approved dissolution acceptance criterion
Source	Apparatus	Media/ Volume	Agitation speed/ Temperature	30 min: NLT (b) (4) % (Q)
In-house	USP apparatus 2	Medium: 0.1 N HCl + 0.2% SLS Volume: 900 mL	Speed: 50 rpm Temp: 37±0.5 °C	

From a Biopharmaceutics perspective, the initial risk is considered to be Medium. Based on the risk mitigation and control strategies, the final risk has been updated to Low (Table 2).

Table 2: Risk Assessment

Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment	Comments
Medium	• The drug product is an immediate release product. • The tadalafil API is a low-solubility drug substance. • The concentration of the (b) (4)	Low	• (b) (4) a three-tier API-PSD has been established to ensure consistent <i>in vitro</i> dissolution and <i>in vivo</i> drug release. • The concentration of (b) (4) has been established to

Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment	Comments
	(b) (4) is a CFV that would impact the <i>in vitro</i> dissolution and <i>in vivo</i> bioavailability.		ensure consistent <i>in vitro</i> dissolution and <i>in vivo</i> drug release. The dissolution method and acceptance criterion possess the ability to discriminate and reject variant and non-bioequivalent batches.

- **Product Bridging:**

Bridging of drug product formulations across product development:

PK studies were conducted on the to-be-marketed (TBM) formulation of the 20 mg strength. Thus, a bridging of formulations for the 20 mg strength is not required. In accordance with 21 CFR 320.22(d)(2), the bridging of the TBM formulations of the 5 mg and 10 mg strengths to the TBM formulation of the 20 mg strength is based on –

- The TBM composition of the 5 mg and 10 mg strengths are proportional to each other, wherein all the active and inactive ingredients are in exactly the same proportion between the 5 mg and 10 mg strengths (the 10 mg strength tablet has twice the active and inactive ingredients of the 5 mg strength tablet).
- The TBM composition of the 5 mg/10 mg strengths are proportionally similar to the TBM composition of the 20 mg bio-strength:
 - The TBM composition of the 5 mg/10 mg strengths differ from the TBM composition of the 20 mg strength in the concentration of (b) (4). The difference in the composition between the TBM formulations of the 5 mg/10 mg and 20 mg strengths is within the (b) (4)% change in the concentration of the (b) (4) and hence is considered as a Level 1 change as per the SUPAC-IR Guidance.
 - The drug product is a high potency drug, where the weight of the active is relatively low (b) (4)% of the tablet (b) (4) weight) when compared to the weight of the dosage form, and the total weight for three strengths is within ±10% of the total weight of the strength used in the BA study, and is thus considered to remain nearly the same.
- PK study# TADA-22-051 on the TBM formulation of the 20 mg strength of the proposed product demonstrating bioequivalence to the 20 mg strength of the LD product.
- Dissolution similarity between all batches of the three strengths as evidenced by $\geq$ (b) (4)% dissolution at the 15-minute time-point without the need for an *f*₂ calculation.

Based on the totality of the submitted data, a bridge between the 5 mg/10 mg TBM formulations and the 20 mg TBM formulation has been satisfactorily established, and an additional *in vivo* BE study for the lower (5 mg and 10 mg) strengths is not required.

Bridging of manufacturing sites and batch sizes:

A single site has been used to manufacture the TBM batches of the 5 mg, 10 mg and 20 mg strengths. PK studies were conducted on the TBM batch of the 20 mg strength. Thus, a bridging of manufacturing sites for the 20 mg strength is not required. Based on the totality of the information submitted in support of the bridging across the formulations, the overall bridging of the manufacturing site for the 5 mg and 10 mg strengths is deemed acceptable.

The sizes of the exhibit and commercial batches are the same (b) (4) Kg for 5 mg strength (b) (4) Kg for the 10 mg strength and (b) (4) Kg for the 20 mg strength). The size of the exhibit/commercial batches of the 5 mg and 10 mg strengths are within 10× the size of batches of the 20 mg bio-strength. Based on the totality of the information submitted in support of the bridging across the formulations, the overall bridging of the products across the batch sizes is deemed acceptable.

- **Biowaiver request:**

The proposed drug product relies in part on the FDA’s prior determination of safety and effectiveness of the Listed Drug (LD), Cialis (Tadalafil) Tablets, 5 mg, 10 mg and 20 mg, (NDA 021368) developed by Eli Lilly and Co. The Applicant has established a clinical “bridge” by conducting single-dose bioavailability studies on the 20 mg strength of the proposed product with the 20 mg strength of the LD. In accordance with 21 CFR 320.22(d)(2), the Applicant requested a biowaiver for the 5 mg and 10 mg strengths based on (i) acceptable bioequivalence studies on the 20 mg strength, (ii) acceptable *in vitro* dissolution testing across all strengths (5 mg, 10 mg and 20 mg), and (iii) proportional similarity of the formulations across all strengths 5 mg, 10 mg and 20 mg.

Based on the totality of the information submitted in support of the bridging across the formulations, manufacturing sites and batch sizes, the data in support of a waiver for demonstration of *in vivo* bioequivalence for the 5 mg and 10 mg strengths in accordance with 21 CFR 320.22(d)(2) is deemed acceptable. An additional *in vivo* study is not required. The efficacy studies for the 5 mg, 10 mg and 20 mg strengths will be assessed by the Clinical/Clinical Pharmacology Reviewer.

The list of submissions assessed in the NDA are shown below in Table 3.

Table 3: List of Submissions Being Assessed

IND/NDA	eCTD sequence #	Date of submission	Document
NDA	0001	8/30/2023	Original Submission

Concise Description of Outstanding Issues (list bullet points with key information and update as needed):

None

OVERALL BIOPHARMACEUTICS RECOMMENDATION:

From a Biopharmaceutics perspective, NDA-218527-ORIG-1 for (b) (4) – Tadalafil Chewable Tablets, 5 mg, 10 mg and 20 mg, is **adequate** and is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

B.1. BCS DESIGNATION:

Assessment: Not Applicable

Solubility:

The active pharmaceutical ingredient (API), tadalafil, is a white or almost white powder that is practically insoluble in water, freely soluble in dimethyl sulfoxide and slightly soluble in methylene chloride. The aqueous solubility profile of the tadalafil drug substance across the physiological pH range (as shown below in Table 4) indicates a pH-independent solubility ranging from 0.0016 mg/mL (0.1 N HCl; pH 1.2) to 0.0025 mg/mL (pH 4.5).

Table 4: Aqueous solubility data of the tadalafil API

pH Buffers	Solubility (mg/mL)
Water	0.0028
0.1 N HCl	0.0016
pH 4.5	0.0025
pH 6.8	0.0023

Permeability:

Being a 505(b)(2) submission, the Applicant did not submit any information on the permeability of the tadalafil drug substance. The Applicant has classified the tadalafil API as a BCS class 2 drug substance.

Reviewer's assessment:

Based on the solubility profile of the tadalafil API across the physiological pH range of 1.2 (0.1 N HCl) to 6.8, at the highest dose strength of 20 mg and the lowest solubility of 0.0016 mg/mL (at pH 1.2 [0.1 N HCl]; Table 4), the volume of solvent required to dissolve the API is (b) (4) mL. Thus, the tadalafil API can be considered to be a low-solubility compound.

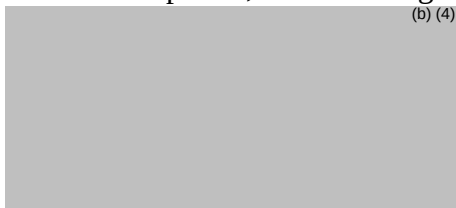
Based on the BCS classification system, the Applicant has classified the tadalafil API as a BCS Class 2 compound. Since the Applicant has not requested a formal claim for the BCS designation, the permeability and BCS class of the tadalafil API have not been assessed.

B.2. DISSOLUTION METHOD AND ACCEPTANCE CRITERION:

Assessment: Adequate

B.2.1. In vitro dissolution method:

During the early stage of the drug product development, dissolution media and volume were established based on the drug substance solubility, immediate release nature of the dosage form and the dissolution method in the USP monograph for Tadalafil tablets. As part of the dissolution method development, the following dissolution parameters were investigated:



(b) (4)

The details are provided in the Dissolution method development report (page 1). The dissolution method adopted by the Applicant for QC of the drug product at release and through the stability program is shown below in Table 5:

Table 5: Proposed dissolution method for QC of the drug product

Apparatus	USP apparatus 2
Media	0.1 N HCl + 0.2% SLS
Media volume	900 mL
Rotation speed	50 rpm
Temperature	37±0.5 °C
Sampling time-points	10, 15, 20, 30, 45 and 60 min

Reviewer's assessment:

Based on the solubility profile of the tadalafil API across the physiological pH range of 1.2 to 6.8, at the highest dose strength of 20 mg and the lowest solubility of 0.0016 mg/mL (at pH 1.2 [0.1 N HCl] Table 4), the volume of solvent required to dissolve the API is (b) (4) mL. Based on the incomplete ((b) (4)%) dissolution of the drug product in media ((b) (4)) and obtain a complete (> (b) (4)%) dissolution is found acceptable.

Discriminating ability of the proposed method: The tadalafil API is a low-solubility drug substance across the physiological pH range of 1.2 to 6.8. Furthermore, the proposed dissolution media contains (b) (4) – SLS at a concentration of 0.2%. Thus, the risk from a Biopharmaceutics perspective is high. As part of the initial risk mitigation strategy, the Applicant identified the Critical Bioavailability Attributes (CBAs) and submitted data demonstrating discriminating ability of the proposed method towards the CBAs on the 20 mg strength of the drug product.

- Effect of Critical Process Parameters (CPPs): The Applicant stated that no CPPs were identified. Hence, the discriminating ability of the method towards variations in the process parameters on was not evaluated.

- b. Effect of Critical Material Attribute (CMAs): The tadalafil API is a low-solubility drug substance, wherein the particle size distribution of the API is a CMA that would impact the in vitro dissolution and bioavailability of the drug product. Based on (b) (4) a three-tier API-PSD being established, the discriminating ability of the method towards variations in the API-PSD on was not evaluated.
- c. Effect of Critical Formulation Variants (CFVs):
- (i) Effect of varying the concentration of (b) (4): The discriminating ability of the method towards variations in the concentration of (b) (4) was initially assessed. Variant batches of the 20 mg bio-strength with a higher (b) (4) and lower concentration (b) (4) of (b) (4) were compared to the batch with optimal concentration (B# RB-0059-015 and Biobatch# EB-797; (b) (4)). The weight of the tablet of the variant batches was maintained by increasing/decreasing the concentration of (b) (4). The composition of the optimal/variant batches and the dissolution data are shown below in Tables 6A and 6B, respectively.

Table 6A: Composition of optimal/variant batches used to demonstrate discriminating ability of the proposed dissolution method

Tadalafil Chewable Tablets, 20 mg										
Batch No.		RB-0059-006	RB-0059-008	RB-0059-009	RB-0059-010	RB-0059-012	RB-0059-013	RB-0059-014	RB-0059-015	RB-0059-016
Item	Ingredients	Mg/Tab	Mg/Tab	Mg/Tab	Mg/Tab	Mg/Tab	Mg/Tab	Mg/Tab	Mg/Tab	Mg/Tab
				(b) (4)						
1	Tadalafil, USP	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
(b) (4)										

Table 6B: Dissolution data of optimal/variant batches and biobatch used to demonstrate discriminating ability of the proposed dissolution method

Batch details	Mean % Dissolved (min)						f2 vs Bio-batch EB-797 (Reviewer calculated)	
	10	15	20	30	45	60	ICH M9	FDA- Guidance
RB-0059-006	(b) (4)						N.C.	51.35
RB-0059-008							N.C.	48.77
RB-0059-009							N.C.	52.74
RB-0059-010							N.C.	50.47
RB-0059-012							N.C.	52.84
RB-0059-013							N.C.	50.22
RB-0059-014							N.C.	52.15
RB-0059-015							N.C.	54.68
RB-0059-016							N.C.	52.15
EB-797							—	—

N.C.: Not Calculated due to insufficient data points (<(b) (4)% dissolution of EB-797 at the first time-point).

Based on the dissolution data, this Reviewer concludes that only one of the variant batches (B# RB-0059-008) exhibits a dissolution profile that differs ($f_2 < 50$) from the biobatch (EB-797). However, based on the composition of all the variant batches (Table 6A), this Reviewer concludes that the proposed method does not possess the ability to discriminate a $\pm 1\%$ difference in the concentration of (b) (4).

- (ii) Effect of exclusion of (b) (4): Based on the lack of discriminating ability of the method with respect to a $\pm 1\%$ difference in the concentration of (b) (4), the Applicant re-evaluated the discriminating ability of the method by manufacturing a variant batch (b) (4) (B# RB-157-072D). The dissolution data is shown below in Table 6C.

Table 6C: Dissolution data of biobatch and variant batch (b) (4) used to demonstrate discriminating ability of the proposed dissolution method

Batch details	Mean % Dissolved (min)						f2 vs Bio-batch EB-797 (Reviewer calculated)	
	10	15	20	30	45	60	ICH M9	FDA- Guidance
RB-157-072D	(b) (4)						N.C.	40.58
EB-797							—	—

N.C.: Not Calculated due to insufficient data points (>(b) (4)% dissolution of EB-797 at the first time-point).

Based on the submitted data, the dissolution profile of the variant batch without (b) (4) (B# RB-157-072D) differs ($f_2 < 50$) from the biobatch (B# EB-797). Although the variant batch (B# RB-157-072D; (b) (4)) is within $\pm 10\%$ – 20% of the biobatch (B# EB-797; (b) (4)), the removal of the (b) (4) is considered less meaningful when demonstrating discriminating ability. Based on the submitted data, this Reviewer concludes that the proposed dissolution method exhibits limited discriminating ability with respect to the concentration of the (b) (4).

- d. Dissolution profiles of BE and non-BE batches: As part of the formulation development, Phase 1 bioequivalence studies were conducted on two test batches of the 20 mg strength (B# RBMP-152-031; Study# TADA-21-079 and Biobatch# EB-797; Study# TADA-22-

051). The composition of B# RBMP-152-031 qualitatively and quantitatively differed from the biobatch (B# EB-797) (Tables 7A and 7B).

Table 7A: Composition of test B# RBMP-152-031; S# TADA-21-079

Batch#		RB-0152-031		Function
Strength		20 mg		
S. No #	Ingredients	mg/tab	% w/w	
(b) (4)				

Table 7B: Composition of the Biobatch# EB-797; S# TADA-22-051

[illegible]

The difference in the composition between the two batches (as summarized below) can be considered as a Level 3 change as per the SUPAC-IR Guidance.

- B# RBMP-152-031 contains (b) (4)
(b) (4)
- BioB# EB-797 contains (b) (4)
(b) (4)

The PK parameters and dissolution data of the test batches (B#s RBMP-152-031 and EB-797) and the LD (B# D247339D) are shown below in Tables 7C and 7D, respectively.

Table 7C: PK parameters of test batches (B#s RBMP-152-031 and EB-797) relative to the LD (B# D247339D)

Batch details	Conditions	PK parameters	Ratio (%) (T/R)	90% CI (T vs. R)	Acceptance criterion	BE outcome
RBMP-152-031 (S# TADA-21-079)	Fasting	C _{max}	66.66	80.4%–73.6%	80%–125%	Not BE
		AUC ₀₋₇₂	88.53	81.4%–96.3%		
	Fed	C _{max}	128.97	112.7%–147.7%		
		AUC ₀₋₇₂	122.39	110.8%–135.2%		
EB-797 (S# TADA-22-051)	Fasting	C _{max}	97.04	91.9%–102.4%		BE
		AUC ₀₋₇₂	97.48	92.4%–102.8%		
	Fed	C _{max}	87.19	80.0%–95.0%		
		AUC ₀₋₇₂	88.53	105.8%–117.9%		

Table 7D: Dissolution data of test batches (B#s RBMP-152-031 and EB-797) and the LD (B# D247339D)

Batch details	Mean % Dissolved (min)						f2 vs LD (B# D247339D) (Reviewer calculated)		f2 vs BioB (B# EB-797) (Reviewer calculated)	
	10	15	20	30	45	60	ICH M9	FDA-Guidance	ICH M9	FDA-Guidance
RB-152-031	(b) (4)						N.C.	34.23	N.C.	43.66
EB-797	(b) (4)						N.C.	N.C.	–	–
D247339D	(b) (4)						–	–	N.C.	N.C.

N.C.: Not Calculated due to insufficient data points (> (b) (4) dissolution of one of the batches at the first/second time-point).

Based on the submitted data, the dissolution profile of the biobatch (B# EB-797) which is BE to the LD (Table 7C) is similar to LD (Table 7D; (b) (4) % dissolution of both products in 15 minutes – without the requirement for an f2 comparison). However, B# RBMP-152-031 which is not BE to the LD (Table 7C) exhibits a dissolution profile that differs (f2 <50) from the LD and the biobatch (Table 7D). Thus, this Reviewer concludes that despite the dissolution medium contains (b) (4) (0.2% SLS), the proposed dissolution method is bio-predictive and possesses the ability to discriminate a non-BE batch.

Based on the totality of the submitted information (listed below), the proposed dissolution method is found acceptable.

- exhibits a complete (> (b) (4) %) dissolution
- exhibits a low inter-vessel variability (<10% RSD) at all the sampling time-points, and
- demonstrates discriminating ability (towards the non-BE batch and a variant batch differing in the concentration of (b) (4))

The inability of the dissolution method to discriminate against minor (Level 1) changes in the composition of the drug product may be attributed to (b) (4). For a low-solubility API, the API-PSD could be the primary CBA. The use of the (b) (4) would ensure consistent *in vitro* dissolution, and render the dissolution method less sensitive to minor (Level 1) changes in the other CBAs – such as CFVs.

B.2.2. Dissolution Data and Acceptance Criterion:

Based on the dissolution method (Table 5), the Applicant submitted the dissolution data of the clinical and registration batches of the 5 mg, 10 mg and 20 mg strengths (see Appendix 1: Table 13). Based on the dissolution data, the acceptance criterion proposed by the Applicant for QC of

the product at release and through the stability program is “Q = (b) (4) in 30 minutes”. The dissolution method and acceptance criterion proposed by the Applicant for QC of the drug product are shown below in Table 8A.

Table 8A: Dissolution method and acceptance criterion proposed by the Applicant and agreed by the FDA

Dissolution method Proposed (seq 0001) and agreed by FDA				Dissolution acceptance criterion Proposed (seq 0001) and agreed by FDA
Source	Apparatus	Medium/ Volume	Agitation speed/ Temperature	30 min: NLT (b) (4)% (Q)
In-house	USP apparatus 2	Medium: 0.1 N HCl + 0.2% SLS Volume: 900 mL	Speed: 50 rpm Temp: 37±0.5 °C	

Reviewer’s assessment:

The proposed drug product an immediate release product with a median T_{max} ranging from 2.67 hours (fasting) to 5.00 hours (fed). Although the drug product is a chewable product, there is no evidence of the drug release and absorption in the buccal cavity. Based on the dissolution data of the clinical and exhibit/registration batches, (b) (4) of the drug product is released at the 30-minute time-point (Table 7D and Appendix 1:Table 13), and possess the ability to comply with the proposed acceptance criterion of “Q = (b) (4)% in 30 minutes” at the S1 stage of testing (Table 8B). The proposed acceptance criterion possesses the ability to reject variant B# RB-157-072D (with a mean dissolution value of (b) (4)% at the 30-minute time-point (Table 6C) – that would require proceeding to the S2 stage of testing; Table 8B) and the non-BE B# RBMP-152-031 (with a mean dissolution value of (b) (4) at the 30-minute time-point (Table 7D) – that would not comply at the S3 stage of testing (Table 8B).

Table 8B: Ability of clinical, variant and non-BE batches to comply with proposed acceptance criterion (based on simulation using the Biopharmaceutics Automation Tool)

BioB# EB-797: Pass rate (%) based on number of simulations specified

Pass Stage 1 (%)	Pass Stage 2 (%)	Pass Stage 3 (%)	No. of simulations	Mean release (%)	CV (%)	Q (%)
100.00	100.00	100.00	1000	(b) (4)	1.1	(b) (4)

Variant B# RB-152-072: Pass rate (%) based on number of simulations specified

Pass Stage 1 (%)	Pass Stage 2 (%)	Pass Stage 3 (%)	No. of simulations	Mean release (%)	CV (%)	Q (%)
0.00	100.00	100.00	1000	(b) (4)	2.5	(b) (4)

Non-BE B# RBMP-152-031: Pass rate (%) based on number of simulations specified

Pass Stage 1 (%)	Pass Stage 2 (%)	Pass Stage 3 (%)	No. of simulations	Mean release (%)	CV (%)	Q (%)
0.00	0.90	0.90	1000	(b) (4)	1.8	(b) (4)

Based on the totality of the submitted information, including the ability to reject the variant and non-BE batches, the proposed dissolution acceptance criterion of “Q = (b) (4)% in 30 minutes” is found acceptable.

Based on the totality of the submitted information, the dissolution method and acceptance criterion as shown above in Table 8A are found acceptable.

B.2.3. Dissolution data during Stability:

Stability studies were conducted on the three exhibit/clinical batches of the 5 mg, 10 mg and 20 mg strength as shown below in Table 9 using the proposed dissolution method/acceptance criterion. Primary stability data was generated under long term (25 °C/60% RH), accelerated (40 °C /75% RH) and intermediate (30 °C/65% RH) storage conditions.

Table 9: Details of batches of the 5 mg, 10 mg and 20 mg strengths placed on stability

Tadalafil Chewable Tablets, 5 mg			
Exhibit Batch	Drug Substance Reference	Drug Product Production	Drug Product Packaging
01	(b) (4)	Batch / Lot EB-794A (Production)	Batch / Lot EB-794A (Packaging)
02		Batch / Lot EB-795A (Production)	Batch / Lot EB-795A (Packaging)
03		Batch / Lot EB-796A (Production)	Batch / Lot EB-796A (Packaging)
Tadalafil Chewable Tablets, 10 mg			
Exhibit Batch	Drug Substance Reference	Drug Product Production	Drug Product Packaging
01	(b) (4)	Batch / Lot EB-800 (Production)	Batch / Lot EB-800 (Packaging)
02		Batch / Lot EB-801 (Production)	Batch / Lot EB-801 (Packaging)
03		Batch / Lot EB-802 (Production)	Batch / Lot EB-802 (Packaging)
Tadalafil Chewable Tablets, 20 mg			
Exhibit Batch	Drug Substance Reference	Drug Product Production	Drug Product Packaging
01	(b) (4)	*Batch / Lot EB-797 (Production)	Batch / Lot EB-797 (Packaging)
02		Batch / Lot EB-798 (Production)	Batch / Lot EB-798 (Packaging)
03		Batch / Lot EB-799 (Production)	Batch / Lot EB-799 (Packaging)

Reviewer's assessment:

The dissolution method and acceptance criterion as shown above in Table 8 have been proposed for the QC of the drug product at release and through the stability period. Assessment of the stability data is under the purview of the CMC/DP Reviewer.

B.2.4. Disintegration method and acceptance criterion:

Being a chewable tablet, in accordance with the August 2018 Guidance for Industry: Quality Attribute Considerations for Chewable Tablets, the Applicant developed a disintegration test under USP <701> and proposed a disintegration acceptance criterion of “NMT (b) (4)” as part of the finished drug product specifications.

Reviewer’s assessment:

For chewable tablets, the disintegration time should be short enough to prevent GI obstruction in the event a tablet is not completely chewed by the patient. Usually, the presence of the correct type and amount of a disintegrant facilitates rapid disintegration of the tablet. In vitro disintegration testing should be conducted using intact tablets in suitable medium using established disintegration equipment (such as USP Disintegration Apparatus) and methods. Assessment of the proposed disintegration method and the disintegration acceptance criterion is under the purview of the CMC/DP Reviewer.

B.3. CLINICAL RELEVANCE OF DISSOLUTION METHOD AND ACCEPTANCE CRITERION (e.g., IVIVR/IVIVC, *In silico* modeling, small scale in vivo):

Assessment: Adequate

Reviewer’s assessment:

The Applicant has not performed an IVIVR/IVIVC nor any modeling studies. The dissolution method proposed by Applicant is to ensure batch-to-batch consistency, and this is acceptable. Based on the Phase 1 PK study on the 20 mg strength of the product (Study# TADA-22-051) the median T_{max} ranges from 2.67 hours (fasting) to 5.00 hours (fed). The relatively long T_{max} for the immediate-release drug product compared to the rapid *in vitro* dissolution (wherein >90% of the product is dissolved at the 30-minute time-point) may be attributed to the presence of (b) (4) (0.2% SLS) in the dissolution medium. Although the dissolution medium contains (b) (4) (0.2% SLS), the proposed dissolution method is bio-predictive and possesses the ability to discriminate a non-BE batch. The proposed acceptance criterion possesses the ability to reject the non-BE batch. Thus, the proposed dissolution method and acceptance criterion mitigate the risk from a Biopharmaceutics perspective to a low level.

B.12. BRIDGING OF PRODUCTS:

Assessment: Adequate

Bridging of Formulations:

PK studies (Study# TADA-22-051 and Study# TADA-23-023) were conducted on the to-be-marketed (TBM) formulation of the 20 mg strength (Table 10). PK studies have not been conducted on TBM formulation of the 5 mg and 10 mg strengths. In accordance with 21 CFR 320.22(d)(2), the Applicant is requesting a biowaiver for the 5 mg and 10 mg strengths based on (i) acceptable bioequivalence studies on the 20 mg strength, (ii) acceptable in vitro dissolution testing across all strengths (5 mg, 10 mg and 20 mg), and (iii) proportional similarity of the formulations across all strengths 5 mg, 10 mg and 20 mg.

Table 10: Composition of the 5 mg, 10 mg and 20 mg strengths of proposed drug product

S. No	Materials	Functions	5 mg		10 mg		20 mg	
			mg/tab	% w/w	mg/tab	% w/w	mg/tab	% w/w
1	Tadalafil, USP	Drug Substance	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
2	Lactose Monohydrate, NF		5.000	(b) (4)	10.000	(b) (4)	20.000	(b) (4)
3	Croscarmellose sodium, NF							
4	FD&C Blue No.1 Aluminum Lake							
5	Sodium Lauryl sulfate, NF							
6	Hydroxypropyl cellulose, NF							
7	(b) (4)							
8								
9								
		(b) (4)	(b) (4)					
10	Maumitol, USP/NF							(b) (4)
11	Microcrystalline Cellulose, NF							
12	Sucralose, NF							
	(b) (4) Bubblegum flavor	(b) (4)						
13	(b) (4)	(b) (4)						
	• Natural and Artificial Flavor	(b) (4)						
14	Colloidal Silicon Dioxide, NF							
15	(b) (4)							
16								
17	Magnesium stearate, NF							
	Total							

Reviewer's assessment:

PK studies were conducted on the to-be-marketed (TBM) formulation of the 20 mg strength. Thus, a bridging of formulations for the 20 mg strength is not required.

In accordance with 21 CFR 320.22(d)(2), the bridging of the TBM formulation of the 5 mg and 10 mg strengths to the TBM formulation of the 20 mg strength is based on –

- The TBM composition of the 5 mg and 10 mg strengths are proportional to each other, wherein all the active and inactive ingredients are in exactly the same proportion between the 5 mg and 10 mg strengths (the 10 mg strength tablet has twice the active and inactive ingredients of the 5 mg strength tablet; Table 10).
- The TBM composition of the 5 mg/10 mg strengths are proportionally similar to the TBM composition of the 20 mg bio-strength:
 - The TBM composition of the 5 mg/10 mg strengths differ from the TBM composition of the 20 mg strength in the concentration of the (b) (4) (b) (4) is present at a concentration of (b) (4) % w/w in the 20 mg strength and at a concentration of (b) (4) % w/w in the 5 mg and 10 mg strengths. A (b) (4) % increase in the concentration of (b) (4) – (b) (4) between the TBM formulations of the 5 mg/10 mg and 20 mg strengths (Table 10) is within the (b) (4) % change in the concentration of the (b) (4), and hence is considered as a Level 1 change as per the SUPAC-IR Guidance.
 - The drug product is a high potency drug, where the weight of the active ((b) (4) % w/w for the 5 mg and 10 mg strengths, and (b) (4) % w/w for the 20 mg strength) is relatively low (b) (4) % of the tablet (b) (4) weight) when compared to the weight of the dosage form, and the total weight for three strengths (b) (4) is

within $\pm 10\%$ of the total weight of the strength used in the BA study and is considered to remain nearly the same¹.

- PK study# TADA-22-051 on the TBM formulation of the 20 mg strength of the proposed product demonstrating bioequivalence to the 20 mg strength of the LD product (Table 7C).
- Dissolution similarity between all batches of the three strengths as evidenced by (b) (4) % dissolution at the 15-minute time-point without the need for an f_2 calculation (Appendix 1: Table 13).

Thus, based on the totality of the submitted data, this Reviewer concludes that a bridge between the 5 mg/10 mg TBM formulations and the 20 mg TBM formulation has been satisfactorily established, and an additional *in vivo* BE study for the lower (5 mg and 10 mg) strengths is not required.

Bridging of Manufacturing sites and Batch sizes: A single site (b) (4) has been used to manufacture the TBM batches of the 5 mg, 10 mg and 20 mg strengths. PK studies were conducted on the TBM formulation of the 20 mg strength. The sizes of the exhibit and commercial batches are the same (b) (4) Kg for 5 mg strength, (b) (4) Kg for the 10 mg strength and (b) (4) Kg for the 20 mg strength). The details of the manufacturing site and size of batches are shown below in Table 11.

Table 11: Details of manufacturing site and size of batches

Manufacturer	Batch size		
All strengths	5 mg	10 mg	20 mg
(b) (4)	(b) (4) Kg (exhibit and commercial)	(b) (4) Kg (exhibit and commercial)	(b) (4) Kg (PK, exhibit and commercial)

Reviewer's assessment:

A single site has been used to manufacture the TBM batches of the 5 mg, 10 mg and 20 mg strengths. PK studies were conducted on the TBM batch of the 20 mg strength. Thus, a bridging of manufacturing sites for the 20 mg strength is not required. Based on the totality of the information submitted in support of the bridging across the formulations, this Reviewer finds the overall bridging of the manufacturing site for the 5 mg and 10 mg strengths to be acceptable.

The sizes of the exhibit and commercial batches are the same (b) (4) Kg for 5 mg strength, (b) (4) Kg for the 10 mg strength and (b) (4) Kg for the 20 mg strength). The size of the exhibit/commercial batches of the 5 mg and 10 mg strengths are within 10× the size of batches of the 20 mg bio-strength. Based on the totality of the information submitted in support of the bridging across the formulations, this Reviewer finds the overall bridging of the products across the batch sizes to be acceptable.

¹ April 2022 Guidance for Industry: Bioavailability Studies Submitted in NDAs or INDs — General Considerations

B.13. BIOWAIVER REQUEST:

Assessment: Adequate

The proposed drug product relies in part on the FDA's prior determination of safety and effectiveness of the Listed Drug (LD), Cialis (Tadalafil) Tablets, 5 mg, 10 mg and 20 mg, (NDA 021368) developed by Eli Lilly and Co. The Applicant has established a clinical "bridge" by conducting two single-dose bioavailability studies on the 20 mg strength of the proposed product with the 20 mg strength of the LD. In accordance with 21 CFR 320.22(d)(2), the Applicant is requesting a biowaiver for the 5 mg and 10 mg strengths based on (i) acceptable bioequivalence studies on the 20 mg strength, (ii) acceptable *in vitro* dissolution testing across all strengths (5 mg, 10 mg and 20 mg), and (iii) proportional similarity of the formulations across all strengths 5 mg, 10 mg and 20 mg.

Reviewer's assessment:

Based on the totality of the information submitted in support of the bridging across the formulations, manufacturing sites and batch sizes, this Reviewer finds the data in support of a waiver for demonstration of *in vivo* bioequivalence for the 5 mg and 10 mg strengths in accordance with 21 CFR 320.22(d)(2) to be acceptable. An additional *in vivo* study is not required. The efficacy studies for the 5 mg, 10 mg and 20 mg strengths will be assessed by the Clinical/Clinical Pharmacology Reviewer.

R. REGIONAL INFORMATION:

Life Cycle Management Considerations and Risk Mitigation Strategies

Reviewer's assessment:

The proposed drug product is an immediate release product wherein the tadalafil API is a low-solubility drug substance. Thus, the particle size distribution (PSD) of the API is a CMA that would impact the dissolution of the drug product. To mitigate the risk from a Biopharmaceutics perspective and ensure consistent drug release *in vitro* and *in vivo*, (b) (4) a three-tier API-PSD being established as shown below in Table 12.

Table 12: PSD (b) (4) tadalafil API

Tadalafil API PSD	
D ₁₀ : NMT	(b) (4) μ
D ₅₀ : NMT	(b) (4) μ
D ₉₀ : NMT	(b) (4) μ

Based on the data demonstrating discriminating ability of the dissolution method, the concentration of the (b) (4) is a CFV. To mitigate the risk from a Biopharmaceutics perspective and ensure consistent drug release *in vitro* and *in vivo*, the concentration of (b) (4) in the drug product has been established at (b) (4) w/w.

The Applicant's approach of establishing a three-tier API-PSD and the concentration of (b) (4), and the ability of the proposed/agreed upon dissolution method and acceptance criterion to discriminate and reject variant and non-BE batches, mitigate the risk from a Biopharmaceutics perspective to a low level.

BIOPHARMACEUTICS PENDING DEFICIENCIES:

None

APPENDIX 1

Data Tables and Figures

The 12-unit dissolution profile data (individual [n], range, %RSD) for the three exhibit/clinical batches of the three (5 mg, 10 mg and 20 mg) strengths of the drug product in the proposed method [USP apparatus 2; 900 mL of 0.1 N HCl + 0.2% SLS; 50 rpm; 37 ± 0.5 °C] is provided in the [link to dissolution data \(page 1\)](#). The mean dissolution data for the three batches of the three (5 mg, 10 mg and 20 mg) strengths is provided below in Table 13.

Table 13: Mean dissolution profile data for the exhibit/clinical batches of the 5 mg, 10 mg and 20 mg strengths in the proposed dissolution method

Strength	Batch details	Mean % Dissolved (min)					
		10	15	20	30	45	60
5 mg	EB-794	(b) (4)					
	EB-795						
	EB-796						
10 mg	EB-800						
	EB-801						
	EB-802						
20 mg	EB-797 (BioB)						
	EB-798						
	EB-799						

f2 comparisons are not required due to >85% dissolution of all batches at the 15-minute time-point. All batches possess the ability to comply with the proposed accepted criterion of "Q = (b) (4) in 30 minutes" at the S1 stage of testing.



Rajesh
Savkur

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