CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218718Orig1s000

PRODUCT QUALITY REVIEW(S)

Title:	NDA IQA Template Title Page-EXEC SUMMARY
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Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	NDA 218718
Applicant Name	Millicent Puerto Rico LLC
Drug Product Name	FEMLYV® (norethindrone acetate/ethinyl estradiol orally disintegrating tablet) 1 mg/20 mcg
Dosage Form	Tablet, orally disintegrating
Proposed Strength(s)	1 mg/20 mcg
NDA Classification	Type 5 – New Formulation or New Manufacturer
Route of Administration	Oral
Maximum Daily Dose	1 mg/20 mcg
Rx/OTC Dispensed	Rx
Proposed Indication	Indicated for use by females of reproductive potential to prevent pregnancy.
Drug Product Description	Millicent Puerto Rico LLC has submitted this 505(b)(2) new drug application for FEMLYV® (norethindrone acetate/ethinyl estradiol orally disintegrating tablet) 1 mg/20 mcg indicated for use by females of reproductive potential to prevent pregnancy. Contraceptives containing these active ingredients have been marketed as brand name and/or generic drug products starting in 1968. FEMLYV® is packaged in blister cards each containing 28 orally disintegrating tablets consisting of 24 green active round orally disintegrating tablets imprinted with “M” on one side and “312” on the other side and 4 white inert orally disintegrating tablets imprinted with “M” on one side and “313” on the other side. The blister cards are packaged in cartons of one or 3 pouches with each pouch containing one blister card.

	Each green active orally disintegrating tablet contains 1mg of norethindrone acetate and 20 mcg of ethinyl estradiol as the active ingredients and croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, mint green lake blend, pregelatinized starch, spearmint flavor, sucralose, and vitamin E (DL-alpha-tocopherol) as inactive ingredients. Each white inert orally disintegrating tablet contains the following inactive ingredients: Croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, pregelatinized starch, spearmint flavor, and sucralose. This drug product should be stored 20°C to 25º C (68°F to 77º F); excursions permitted to 15°C to 30º C (59°F to 86º F) with currently granted expiration dating period of 24 months.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	Store at 20°C to 25º C (68°F to 77º F); excursions permitted to 15°C to 30º C (59°F to 86º F) [See USP Controlled Room Temperature].		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sukhamaya Bain, Ph.D.	Lawrence Perez, Ph.D.
	Drug Product/ Labeling	Caroline Strasinger, Ph.D.	Hamid Shafiei, Ph.D./Julia Pinto, Ph.D.
	Manufacturing	Wei Yang, Ph.D.	Jean Tang, Ph.D.
	Biopharmaceutics	Bryan Ericksen, Ph.D.	Okponanabofa Eradiri, Ph.D.
	Microbiology	N/A	N/A
	Other (specify) Categorical Exclusion	Caroline Strasinger, Ph.D.	Hamid Shafiei, Ph.D.

	RBPM	Stephanie Ngan, MPH
	ATL	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 PI labeling as well as container and carton 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 PI labeling as well as container and carton labels are considered adequate. No additional labeling memorandum will be attached to the labeling review chapter.

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 substances, norethindrone acetate and ethinyl estradiol and the drug product, FEMLYV® (norethindrone acetate/ethinyl estradiol orally disintegrating tablet) 1 mg/20 mcg.
- 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 applicant through 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.

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 - Adequate

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 and Date:

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

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	218718
Assessment Cycle Number	1
Drug Product Name	FEMLYV (norethindrone acetate and ethinyl estradiol orally disintegrating tablets)

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	**9 (30-APR-2024)**
Patient Information	N/A	
Instruction for Use (IFU)	N/A	
Container Labels	Adequate	**10 (7-MAY-2024)**
Carton Labeling	Adequate	**10 (7-MAY-2024)**

Brief Description of Outstanding Issues:

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0009	30-APR-2024	Revised PI
0010	7-MAY-2024	Revised Carton and Container

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

[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)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

On 3/22/24 OPPQ agreed with DMEPA and OND that dropping the trailing 0 on 0.020 mg ethinyl estradiol was acceptable citing the Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. The strength used for this product will be 1 mg/0.2 mg.

- The OPQ Drug Product review team had raised concerns when transitioning from 20 mcg to 0.02 mg instead of 0.020 mg related to significant figures and rounding. For example, a future generic manufacturer could formulate their product with either 15 mcg (i.e., 0.015) or 24 mcg (i.e., 0.024) but still match the strength of 0.02 mg. With manufacturing variability (+-10%) built around those new targets, it could lead to generic drift.

(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)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	
Route(s) of administration	Adequate	(b) (4) Applicant agreed to this change on 30-APR-2024
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)]		

[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).

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 form(s)[4] and strength(s) in metric system[5]	Adequate	(b) (4) (b) (4) strength should be in mg Applicant agreed to this change on 30-APR-2024
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]	Adequate	(not scored)
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*

Applicant agreed to all OPQ requested changes on 30-APR-2024.

[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>
[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]

N/A

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[10]

(b) (4)

[redacted]

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	Orally disintegrating tablets Applicant agreed to this change on 30-APR-2024
Strength(s) in metric system	Adequate	mg presentation for EE Applicant agreed to this change on 30-APR-2024

[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] 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)
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 color and clarity of the solution, when applicable.	Adequate	Formatting changes requested to align more closely to Labeling Review Tool. Applicant agreed to this change on 30-APR-2024
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*

The applicant agreed to all requested OPQ changes on 30-APR-2024.

1.2.3 Section 11 (DESCRIPTION)[11]

(b) (4)

[redacted]

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		

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

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)
Proprietary and established name(s)[12] [§ 201.57(c)(12)(i)(A)].	Adequate	Include established name Applicant agreed to this change on 30-APR-2024
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	Add dosage form Applicant agreed to this change on 30-APR-2024
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.[13] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	List in alphabetical order, use lower case text Applicant agreed to this change on 30-APR-2024
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	N/A	

[12] 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).

[13] 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, 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.

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)
terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].		
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[14] [§ 201.57(c)(12)(i)(E)].	Adequate	Adjust to "combined hormonal contraceptive" Applicant agreed to this change on 30-APR-2024
Chemical name[15], 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[16] (if applicable).	N/A	No voluntary statement is made for this product.
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	Adequate	
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*

[14] 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.

[15] 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).

[16] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

The applicant agreed to the OPQ requested changes on 30-APR-2024.

(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)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	Add dosage form Applicant agreed to this change on 30-APR-2024
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	mg amount needed Applicant agreed to this change on 30-APR-2024
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	Presentation is incorrect, it is a carton, with 3 pouches, each pouch with a blister card of 28 tablets

[17] 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)
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	Formatting Applicant agreed to this change on 30-APR-2024
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	
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	Add [See USP Controlled Room Temperature Storage] Applicant agreed to this change and adjusted the excursion temperatures to 15°C to 30°C (59°F to 86°F) on 30-APR-2024
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	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)
natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[18]		
Include information about child-resistant packaging[19] (if chosen by manufacturer).	N/A	

Assessment: *Adequate*

The applicant agreed to all OPQ requested changes and incorporated them into the labeling on 30-APR-2024.

1.2.6 Manufacturing Information After Section 17 (for drug products)[20]

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	Distributed by: Millicent U.S., Inc. East Hanover, NJ 07936

Assessment: *Adequate*

3.0 CONTAINER AND CARTON LABELING[21] (The below labels were provided in the original submission. On 07-MAY-2024, the Applicant provided updated labels incorporating all OPQ requested changes. The updated labels can be found in the Appendix of this review for ease of reference).

[18] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[19] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[20] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)
[21] Carton and Container Labeling Resources

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

Item	Item in Proposed Carton 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[23], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	In the established name replace "/" with "and" Applicant agreed to this change on 7-MAY-2024
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[24]	Adequate	Yes	Change 20 mcg to 0.02 mg Applicant agreed to this change on 7-MAY-2024
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	N/A	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>].	N/A	Choose an item.	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[25]	Adequate	No	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	No	DMEPA to address the need for differing carton and pouch NDC numbers (if applicable)
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	Include the lot number and expiration date on the pouch Applicant agreed to this change on 7-MAY-2024
Storage conditions. If applicable, include a space on	Adequate	Yes	

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

[24] 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)

[25] § 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.

Item	Item in Proposed Carton 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)
the carton labeling for the user to write the beyond-use-date (BUD).			
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)].	Adequate	Yes	Oral drug therefore list of excipients not required
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)].[26]	Adequate	Yes	

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

Item	Item in Proposed Carton 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)
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
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	Yes	
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 overseal 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.	
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.[27]	N/A	Choose an item.	

[27] USP General Notices 3.20 Indicating Conformance

Item	Item in Proposed Carton 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)
And others if space is available.	N/A	Choose an item.	

Assessment of Carton Labels and Container Labeling: *Adequate*
The below information was communicated with the OSE/DMEPA comments for the container closure system. The applicant agreed to all OPQ requested changes and incorporated them into the Carton, Pouch, and Blister Card on 07-MAY-2024.

The following apply to the Carton, Pouch, and Blister Card

- **In the established name presentation, replace "/" with "and" so that the established name reads "norethindrone acetate and ethinyl estradiol orally disintegrating tablets"**
- **Revise the strength of both active ingredients to be presented as mg amounts (i.e., 1 mg and 0.02 mg respectively)**

On the Pouch

- **Include the lot number and expiration date**

On the Carton and Pouch

- **Remove (b) (4) from the following sentence "Each blister card contains 24 green tablets and 4 white (b) (4) tablets."**

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

None. Applicant has agreed to all OPQ requested changes. The Label and Labeling for NDA 218718 is now adequate.

Primary Labeling Assessor Name and Date:

Caroline Strasinger, PhD
Master Reviewer
OPQ/OPQAII/DPQAVII

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Julia Pinto, PhD
Supervisor
OPQ/ OPQAII/DPQAVIII

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Caroline Strasinger

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Julia Pinto

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CHAPTER VI: BIOPHARMACEUTICS

For more details about the items in this template, please see Chapter VI (Biopharmaceutics) of the NDA IQA Guide

NDA Number	NDA-218718-ORIG-1
Assessment Cycle Number	1
Drug Product Name / Strength	Norethindrone Acetate/Ethinyl Estradiol Orally Disintegrating Tablets/ 1 mg/20 mcg
Route of Administration	Oral
Applicant Name	Millicent Puerto Rico LLC
Therapeutic Classification/ OND Division	CDER/OND/ORPURM/DUOG
RLD/RS Number	203667
Proposed Indication	For use by females of reproductive potential to prevent pregnancy.

Assessment Recommendation: **Adequate**

Assessment Summary:

This drug product is indicated for use by females of reproductive potential to prevent pregnancy.

1) Proposed dissolution method and acceptance criterion

The Applicant used the FDA Dissolution Database method for norethindrone acetate/ethinyl estradiol chewable tablet and justified the use of surfactant and 75 RPM paddle speed based on (b) (4) (b) (4) Use of this method is adequate. The Applicant proposed dissolution acceptance criterion of Q= (b) (4)% in 15 minutes for both drug substances, which is acceptable. Dissolution of three batches using the quality control dissolution method was very rapid (>85% in 15 minutes).

2) Formulation bridging

Bridging of formulations is not necessary.

Conclusion

From a Biopharmaceutics perspective, NDA 218718 for NA/EE Orally Disintegrating Tablets, 1 mg/20 mcg, is **ADEQUATE**.

List Submissions Being Assessed:

Document(s) Assessed	Date Received
NDA 218718/Sequence 0001/Original Submission	09/27/2023
NDA 218718/Sequence 0008/Response to Information Request	04/24/2024

Concise Description of Outstanding Issues: NA

B.1 BCS DESIGNATION

Assessment: Both drug substances are highly soluble (BCS Class I or III)

Solubility: Solubility of NA in various buffers is given in Table 1.

Table 1: NA solubility results

NA Solubility - mcg/ml			
Timepoint (hours)	**pH - 1.2 (0.1N HCl)**	**pH - 4.5 (0.1M Sodium Acetate)**	**pH - 6.8 (0.1M Sodium Phosphate)**
1	6.1	6.6	4.9
2	6.2	6.9	5.0
4	6.2	6.8	5.1
24	6.6	6.9	5.5
48	6.7	6.9	5.4

Total solubility of NA in 250 ml is given in Table 2.

Table 2: Total solubility of NA

NA Total Solubility – mg in 250 ml			
Timepoint (hours)	**pH - 1.2 (0.1N HCl)**	**pH - 4.5 (0.1M Sodium Acetate)**	**pH - 6.8 (0.1N Sodium Phosphate)**
1	1.54	1.65	1.22
2	1.55	1.72	1.25
4	1.56	1.70	1.28
24	1.65	1.72	1.37
48	1.67	1.73	1.35

The lowest number in Table 2 is 1.22 mg, which is higher than 1 mg, the maximum daily dose of NA. Therefore, NA is considered highly soluble according to BCS.

Solubility of EE is given in Table 3.

Table 3: EE solubility results

EE Solubility - mcg/ml			
Timepoint (hours)	**pH - 1.2 (0.1N HCl)**	**pH - 4.5 (0.1M Sodium Acetate)**	**pH - 6.8 (0.1M Sodium Phosphate)**
1	10.6	10.5	6.6
2	10.4	11.0	7.9
4	10.8	10.9	8.0
24	10.6	12.3	8.3
48	11.9	12.1	10.0

Total solubility of EE in 250 ml is given in Table 4.

Table 4: Total solubility of EE

EE Solubility – mg in 250 ml			
Timepoint (hours)	pH - 1.2 (0.1N HCl)	pH - 4.5 (0.1M Sodium Acetate)	pH - 6.8 (0.1N Sodium Phosphate)
1	2.66	2.62	1.65
2	2.60	2.74	1.99
4	2.70	2.73	1.99
24	2.64	3.07	2.06
48	2.97	3.01	2.49

The lowest number in Table 4 is 1.65 mg, which is higher than 20 mcg, the maximum daily dose of EE. Therefore, EE is considered highly soluble according to BCS.

Permeability: No data submitted

Dissolution: Dissolution is very rapid in 0.025 M Acetate Buffer, pH 5.0 with 0.15 % SLS, giving > 85% dissolution in 10 minutes for both NA and EE.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

Dissolution Method Development

Complete dissolution data were submitted in Sequence 0008, Module 5.3.1.3 for three batches of the proposed drug product. NA data:

Method Source	USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Sampling Times	Acceptance criteria
FDA	2 (Paddle)	75	0.025 M Acetate Buffer, pH 5.0 with 0.15 % SLS/37 ± 0.5 °C	600	10, 15, 20, 30, 45, and 60 minutes	Q= (b)(4) % in 15 minutes for both NA and EE

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EE data: \\CDSESUB1\evsprod\NDA218718\0008\m5\53-clin-stud-rep\531-rep-biopharm-stud\5313-in-vitro-in-vivo-corr-stud-rep\mp0008-ee\mp0008ee-individ-vessel-data.xlsx

The Applicant used the FDA Dissolution Database method for NA/EE chewable tablet as shown in the following table:

Both the 75 RPM paddle speed and presence of surfactant were justified based on their effect on (b) (4) in the dissolution method development report submitted in Sequence 0008, Module 3.2.R, as shown in Figures 1 and 2:

(b) (4)

A pharmacokinetic study conducted to compare the bioavailability of MP0008 NA & EE ODT vs Minastrin that Cmax was achieved for both APIs by approximately 80 minutes with a time range of 40-150 minutes for NA (assessed as Norethindrone) and 40-122 minutes for EE. For both APIs, measurable concentrations were observed at the first timepoint (20 minutes).

Reviewer Assessment

The Applicant adequately justified the presence of surfactant and 75 RPM paddle speed based on the effect of these parameters on (b) (4).

Dissolution Data

Dissolution data for three batches are shown in Figures 3 and 4.

Figure 3: Mean NA dissolution data for three batches at release

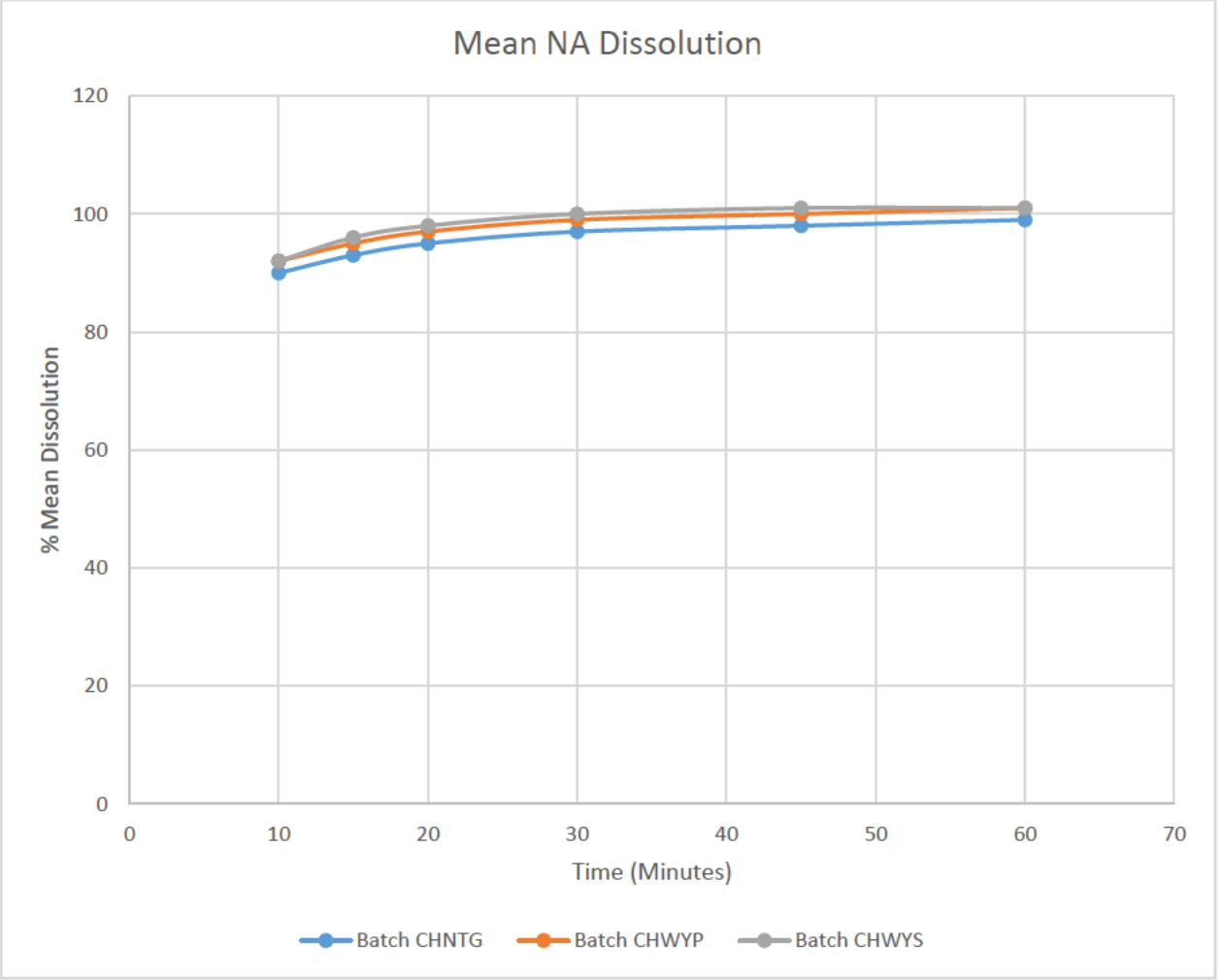
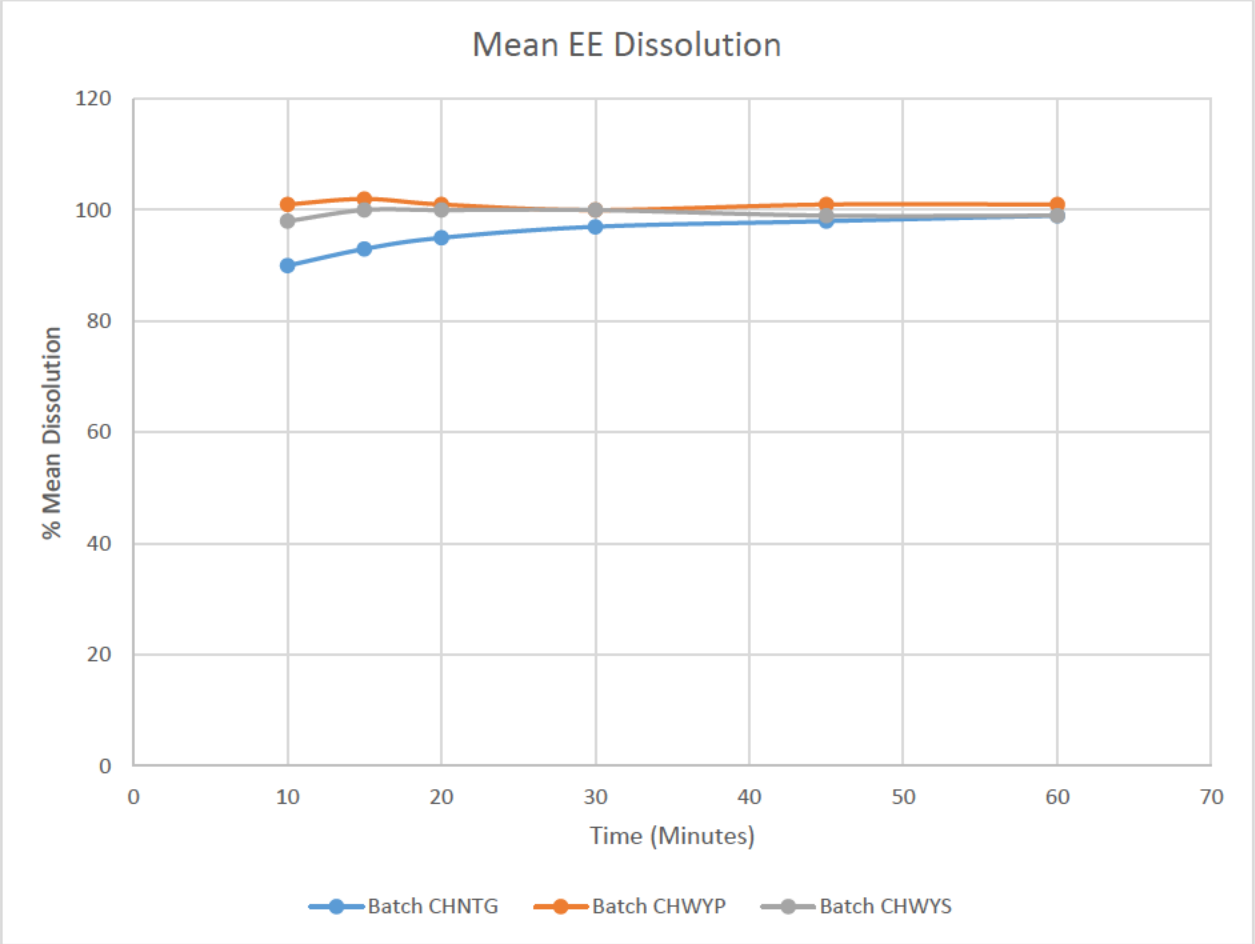


Figure 4: Mean EE dissolution data for three batches at release



Dissolution Acceptance Criteria

The Applicant proposed acceptance criteria of Q=(b)(4)% in 15 minutes for both NA and EE.

Reviewer Assessment

Dissolution of all batches was very rapid for both NA and EE, with greater than 85% dissolution in 15 minutes, as is appropriate for drug substances with high solubility. Therefore, the proposed acceptance criteria are adequate.

B.12 BRIDGING OF FORMULATIONS

N/A

Primary Biopharmaceutics Assessor's Name and Date:
Bryan Ericksen, Ph.D. 04/29/2024

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Okponanabofa Eradiri, Ph.D.

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