CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217639Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	217639		
Applicant Name	Stemline Therapeutics, Inc.		
Drug Product Name	ORSERDU® (elacestrant)		
Dosage Form.	Tablet		
Proposed Strength(s)	345 mg and 86 mg		
Route of Administration	Oral		
Maximum Daily Dose	345 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	ORSERDU is a selective estrogen receptor antagonist indicated for treatment of postmenopausal women and men, with (b) (4)-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy		
Drug Product Description	345 mg: immediate release, light blue, unscored, oval film-coated biconvex tablet, imprinted with “MH” on one side and plain on the other side. 86 mg: immediate release, light blue, unscored, round film-coated biconvex tablet, imprinted with “ME” on one side and plain on the other side.		
Co-packaged product information	N/A		
Device information:	Elacestrant, IR-film coated tablets, 86 mg and 345 mg are packaged in high density polyethylene (HDPE) bottles with child-resistant (CRC) (b) (4) closures that incorporate an induction heat seal liner.		
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F). Excursions permitted from 15°C to 30°C (59°F to 86°F). [see USP controlled room temperature]		
Review Team	**Discipline**	**Primary**	**Secondary**

	Drug Substance	Sivakoteswara Rao Mandadapu	Paresma Patel
	Drug Product/ Labeling	Rajiv Agarwal	Xing Wang
	Manufacturing	Huiquan Wu	Zhaoyang Meng
	Biopharmaceutics	Qi Zhang	Anitha Govada
	Microbiology	Huiquan Wu	Zhaoyang Meng
	Other (specify):	N/A	
	RBPM	Kristine Leahy	
	ATL	Xing Wang	
Consults	N/A		

2. Final Overall Recommendation - *Approval*

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The applicant provided sufficient information to assure the identity, strength, purity, quality, and bioavailability of the proposed drug product. The labels and labeling include adequate quality information as required. All associated manufacturing, testing, packaging facilities were deemed acceptable.

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): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Xing Wang

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CHAPTER IV: LABELING

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

1.0 PRESCRIBING INFORMATION (ONLY primary secondary labels are needed to complete this review. Cut and paste section 11 and 16 too)

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items 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		
Established name(s)[1]	Adequate	Elacestrant
Route(s) of administration	Adequate	Oral
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	86 and (b) (4) mg tablets
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	Not applicable
For injectable drug products for parental 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.	N/A	Not applicable
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	Adequate	**Comment:** This information is in the USPI (in section 11) and bottle labels.

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

ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items 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, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	Not applicable
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Swallow tablets whole. Do not split, crush, or chew tablets.
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	Not applicable
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	N/A	Not applicable

section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	Not applicable
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	Not applicable

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items 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	Tablets
Strength(s) in metric system	Adequate	86 and 345 mg
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 (Tablets: 10 mg of drug-x hydrochloride).	N/A	**Note:** An equivalency statement is added to the USPI (section 11) and on bottle labels.
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	• 345 mg: (b) (4) light blue, unscored, oval film-coated biconvex tablet, imprinted with "MH" on one side and plain on the other side. • 86 mg: (b) (4) light blue, unscored, round film-coated biconvex tablet, imprinted with "ME" on one side and plain on the other side.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not applicable
For injectable drug products for parental 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.	N/A	Not applicable

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Item	Items 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)	Adequate	Elacestrant
Dosage form(s) and route(s) of administration	Adequate	Tablets/Oral
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)"	Adequate	This information is on the USPI and bottle labels.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Yes
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.	N/A	Not applicable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Not applicable
Sterility statement (if applicable)	N/A	Not applicable
Pharmacological/Therapeutic class	Adequate	Not provided and will be communicated to the Applicant by OND
Chemical name, structural formula, molecular weight	Adequate	Yes
If radioactive, statement of important nuclear characteristics.	N/A	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Adequate	Yes

Section 11 (DESCRIPTION) Continued

Item	Items 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)
For oral prescription drug products, include gluten statement (if applicable)	N/A	Not applicable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	Not applicable
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	Not applicable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Item	Items 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)	Adequate	Tablets
Strength(s) in metric system	Adequate	86 and 345 mg
Available units (e.g., bottles of 100 tablets)	Adequate	30 tablets
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Yes
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not applicable
For injectable drug products for parental 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.	N/A	Not applicable
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."	N/A	Not applicable

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items 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)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	**Storage condition is modified and will be communicated to the applicant by OND**
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: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	Not applicable
Include information about child-resistant packaging	Inadequate	**Comment is in place about CRC statement and will be communicated to the applicant by OND**

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items 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)
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	**Manufactured for:** Stemline Therapeutics, Inc., New York, NY 10022 **Manufactured by:** (b) (4) (b) (4)

2.0 PATIENT LABELING

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	Yes
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	**Storage condition is modified and will be communicated to the applicant by OND**
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 differs from the dosage form.	N/A	Not applicable
Active ingredient(s) (if applicable)	Adequate	Yes
Alphabetical listing of inactive ingredients (if applicable)	Adequate	Yes
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Yes

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

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

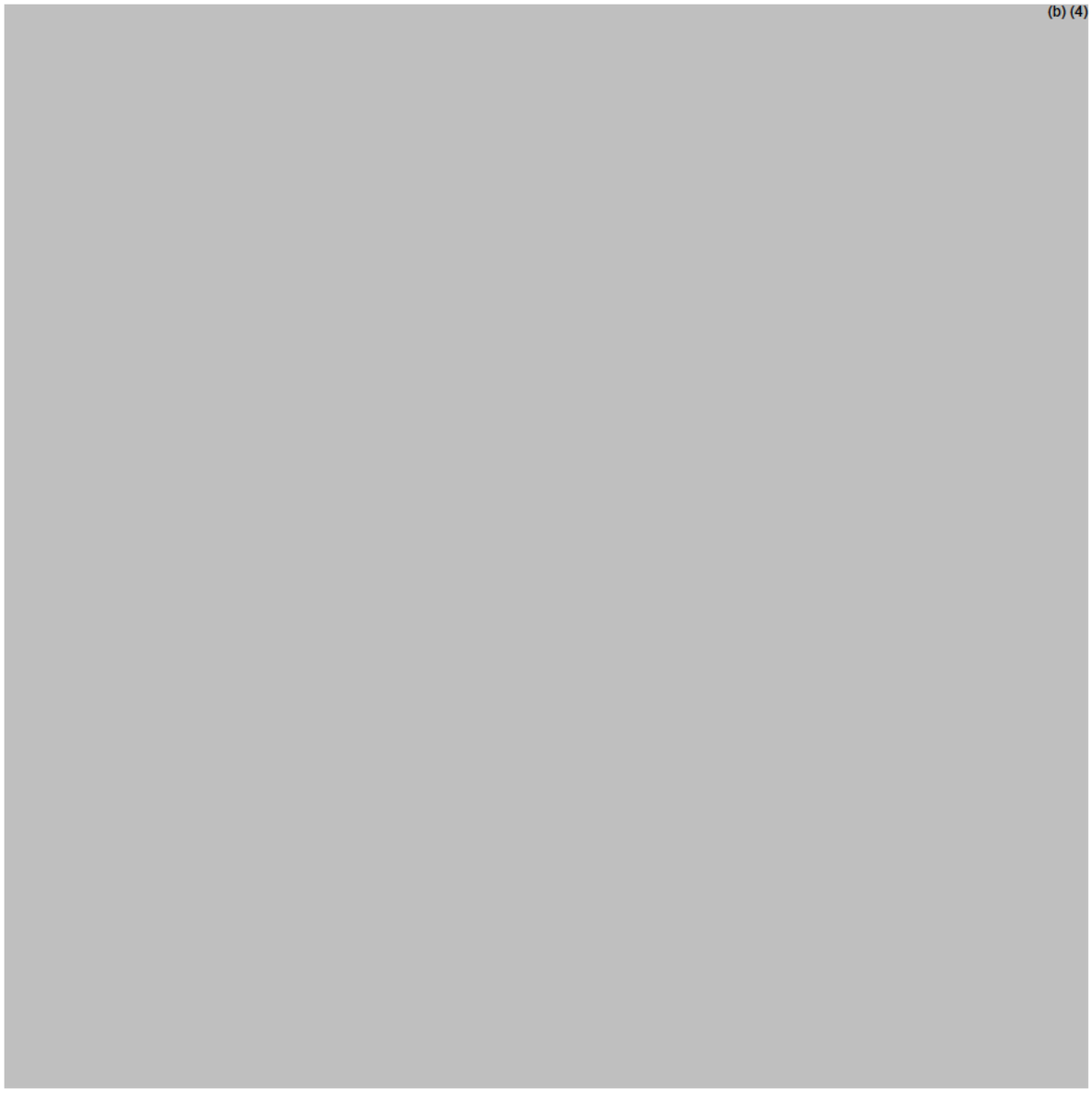
3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels (Bottle)

(Copy/paste or refer to a representative example of a proposed container)

86 and 345 mg tablets

(b) (4)



3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

There are no Cartons.

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	Yes
Strength(s) in metric system	Adequate	Yes
Route(s) of administration	Adequate	Yes
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	Yes
Net contents (e.g., tablet count, volume of liquid)	Adequate	Yes
"Rx only" displayed on the principal display	Adequate	Yes
NDC	Adequate	Yes
Lot number and expiration date	Adequate	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	**Storage condition is modified and will be communicated to the applicant by OND**
For injectable drug products for parental 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.	N/A	Not applicable
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Not applicable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Not applicable
Linear Bar code	Adequate	Yes

3

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	Yes
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	Yes
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	Not applicable
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Not applicable
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.	N/A	Not applicable
And others, if space is available.	N/A	

- **Assessment of Carton and Container Labeling:** ***{Adequate }***
- ***Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."***

Proposed edits in the Description and How supplied sections and bottle labels will be conveyed to the applicant by the OND.

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation:

- Adequate

Primary Labeling Assessor Name and Date: Rajiv Agarwal 9/20/2022

Secondary Assessor Name and Date: Xing Wang, Ph.D

Rajiv Agarwal

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	217639; 505 b (1)-NME
Assessment Cycle	1
Drug Product Name/ Strength	ORSERDU® (elacestrant) tablets 86 mg and 345 mg[1]
Dosage and Administration	Oral Tablet (345 mg orally once daily (b) (4)); administered whole (tablets should not be chewed, crushed, or split prior to swallowing).
Applicant Name	Stemline Therapeutics, Inc.
Associated INDs	IND 124748
Proposed Indication	ORSERDU is a selective estrogen receptor antagonist indicated for treatment of postmenopausal women and men, with (b) (4) HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.

Assessment Recommendation: Adequate

Assessment Summary:

The Applicant, Stemline Therapeutics, is seeking approval of the proposed ORSERDU™ (elacestrant) Tablets, 86 mg, and 345 mg for the treatment of (b) (4) -positive, HER2-negative advanced or metastatic breast cancer. Elacestrant is a selective estrogen receptor antagonist, new molecular entity (NME) developed under IND 124748. The elacestrant dihydrochloride is a BCS Class 4 drug substance. The proposed Elacestrant Tablet is an immediate release (IR), unscored, blue to light blue film coated tablet containing 86 mg (86 (b) (4) mg) or 345 mg (345 (b) (4) mg) of elacestrant (free base). The clinical program in support of this NDA includes a pivotal phase 3 study (RAD1901-308) and 2 supportive phase 1 studies (Study 005 and Study 106) and a pivotal BE study (RAD1901-116).

The Biopharmaceutics review is focused on evaluation of (i) the adequacy of the proposed dissolution method and acceptance criterion, (ii) bridging throughout the drug product development, and (iii) risk assessment.

1) Dissolution Method and Acceptance Criterion

The proposed in vitro dissolution method and the revised dissolution acceptance criterion shown in the table below are approved for the dissolution testing of Elacestrant Tablets, for drug product batch release and stability testing:

[1] 86 mg and 345 mg of elacestrant free base equivalent to 100 mg and 400 mg of elacestrant dihydrochloride respectively. Throughout this review, the drug product 100 mg (equivalent 86 mg free base) and 400 mg (equivalent 345 mg free base) elacestrant dihydrochloride is used.

Approved Dissolution Method and Acceptance Criterion for ORSERDU™ (elacestrant) tablets, 86 mg, and 345 mg				
Apparatus	Speed	Medium	Volume/Temp	Acceptance Criterion
USP Apparatus 2 (Paddle)	*75 rpm*	*0.01 N HCl*	*86 mg: 500 mL/37℃ 345 mg: 1000 mL/37℃*	*NLT (b)(4)%(Q) in 30 minutes*

2) Bridging Throughout Product Development

The proposed commercial Elacestrant Tablets have different formulation and a different product manufacturing site compared to the pivotal phase 3 drug product. Bridging between the clinical and commercial drug products has been established based on the pivotal clinical BE study [RAD1901-116]. Refer to the OCP Review for the supporting PK data.

3) Biopharmaceutics Risk Assessment

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #	Comments
Dissolution	Moderate	BCS Class 4 drug; exhibits pH dependent and low solubility at higher pHs (~0.01 mg/mL at pH 6.8); exhibits polymorphism. (b)(4) No clinically significant effects of food or antiacid on elacestrant.	Low	The risk is mitigated with the implementation of the approved dissolution method and acceptance criterion of Q= (b)(4)% at 30 minutes. Additionally, (b)(4) drug substance and drug product controls (b)(4) are controlled for the proposed drug product.

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Original Submission	2022-06-17 (SDN-01)
Response to Information Request – dissolution method	2022-10-05 (SDN-29)
Response to Information Request – dissolution method	2022-10-14 (SDN-35)
Response to Information Request – dissolution acceptance criterion	2022-11-07 (SDN-43)

Concise Description of Outstanding Issues:

None.

B.1 BCS DESIGNATION

Assessment: *A BCS designation is not requested nor required.*

The Applicant claimed that elacestrant dihydrochloride is a BCS Class 4 drug with low solubility and low permeability because elacestrant dihydrochloride exhibits low solubility at higher pHs (~0.01 mg/mL at pH 6.8) and low permeability (0.17×10^{-6} and 0.89×10^{-6} cm/s at 10 and 100 µM, respectively) based on a Caco-2 cell assay.

Solubility: Elacestrant dihydrochloride was identified (b) (4) and it has been used in clinical supplies and registration stability batches. The Applicant submitted the solubility data (**Table 1**) for elacestrant dihydrochloride drug substance at different pH values.

Table 1: Elacestrant Equilibrium Solubility in Various Media at 37 °C

Media			Prep.	Elacestrant Dihydrochloride Drug Substance Equilibrium Solubility in Various Dissolution Media at 37°C		
pH	Actual pH	Dissolution Media		Solubility (mg/mL)		pH of Solution
				Individual	Mean	
1.2	1.15	0.1 N HCl	1	33.139	32.71	0.97
			2	32.776		0.99
			3	32.227		1.00
2.0	2.02	0.01 N HCl	1	52.968	52.01	1.92
			2	52.788		1.85
			3	50.272		1.91
4.5	4.54	50mM Sodium Acetate Buffer	1	4.515	4.48	4.39
			2	4.510		4.42
			3	4.406		4.43
5.9	5.85	50mM Sodium Phosphate Buffer	1	0.048	0.05	5.47
			2	0.049		5.53
			3	0.047		5.48
6.8	6.76	50mM Sodium Phosphate Buffer	1	0.006	0.01	6.58
			2	0.005		6.64
			3	0.005		6.68

Ref: Table 25 of 3.2.P.2.2

Elacestrant dihydrochloride exhibits pH-dependent solubility and the highest equilibrium solubility (52.01 mg/mL) was observed in the proposed dissolution medium (0.01 N HCl, pH 2.0). The solubility data are consistent with the indicated BCS class of the drug substance because the solubility is 0.05 at pH 5.85 and 0.01 mg/mL at pH 6.8, whereas the minimum required solubility is 1.6 mg/mL in 250 mL for the single 400 mg-dose.

Permeability: The apparent permeability (Papp) values were measured with the absorptive (apical to basolateral) permeability of 017 and 0.89× 10^{-6} cm/sec at drug concentrations of 10 and 100 µM and secretory (basolateral to apical) permeability of 0.86, 0.22, and 0.61 × 10^{-6} cm/sec, at 1 µM, 10 µM, and 100 µM of elacestrant, respectively. The efflux ratios were 1.3 and 0.7 in Caco-2 cells for elacestrant at 10 and 100 µM, respectively, indicating that elacestrant was not a substrate of efflux transporters, eg, P-glycoprotein (P-gp; efflux ratio < 2 at 10 to 100 µM).

The oral absorption of elacestrant was rapid (time to reach maximum concentration [tmax]< 4 hours), with an absolute bioavailability of approximately 10%. According to the labeling, approximately 81.5% ((b) (4) as unchanged) of the dose was recovered in feces and 7.53% in urine ((b) (4) % unchanged) following a single oral dose of of 345 mg radiolabeled elacestrant.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Assessment: *Adequate*

Drug Product: The proposed commercial elacestrant tablet is a debossed, unscored, blue film-coated tablet containing active ingredient elacestrant dihydrochloride, microcrystalline cellulose and silicified microcrystalline cellulose as (b) (4) crospovidone as (b) (4) and magnesium stearate as (b) (4) The total weight of the tablet is 185 mg and 740 mg for the 86 mg and 345 mg, respectively. The drug product is manufactured by a (b) (4)

The drug product is dissolving in 30 minutes using the proposed dissolution method.

Dissolution Method:

The proposed dissolution method parameters (**Table 2**) are selected based on suitability for routine QC testing (complete and robust dissolution and discriminating capability) for Elacestrant Tablets. Refer to the dissolution method development studies as summarized in the Pharmaceutical Development 3.2.P.2.2. and the Applicant Responses to Information Requests (SDN-29 and SDN-35) for detailed information, additional supporting figures, and tables.

Table 2. Proposed Dissolution Method Parameters

Parameters	**Conditions**
Apparatus	USP Apparatus 2 (paddles)
Sample	Each of six single tablets using sinkers
Dissolution media/vessel temperature	37.0 °C (b) (4) °C
Dissolution media volume	500 mL for 100 mg tablets, 1000 mL for 400 mg tablets
Dissolution medium	0.01N HCl
Paddle rotation speed	75 rpm
Pull volume	5 mL (filtered through (b) (4) filter), no media replacement
Sampling time Point	5, 10, 15, 30, 45, 60 (∞) minutes

(b) (4)

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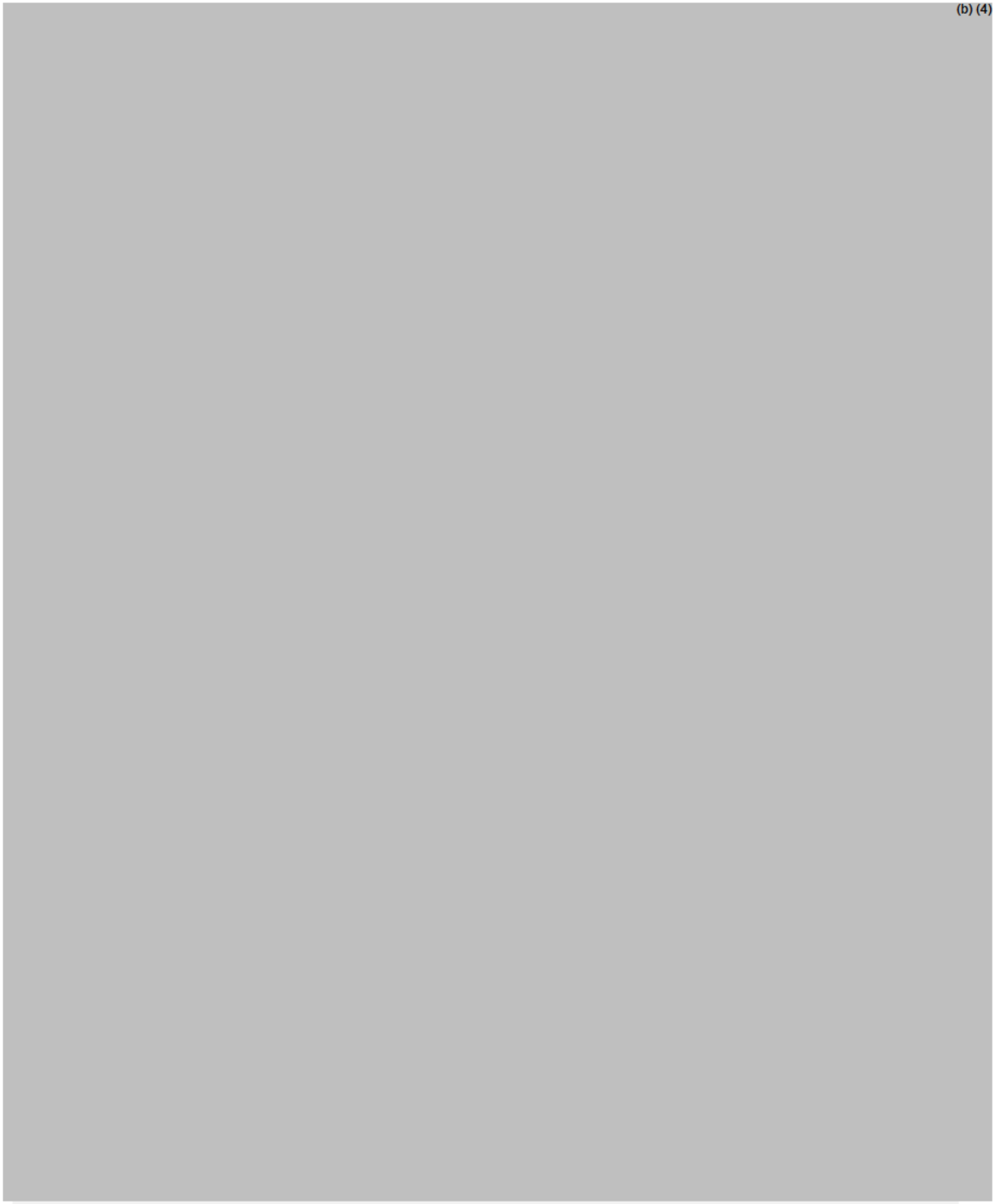
(b) (4)

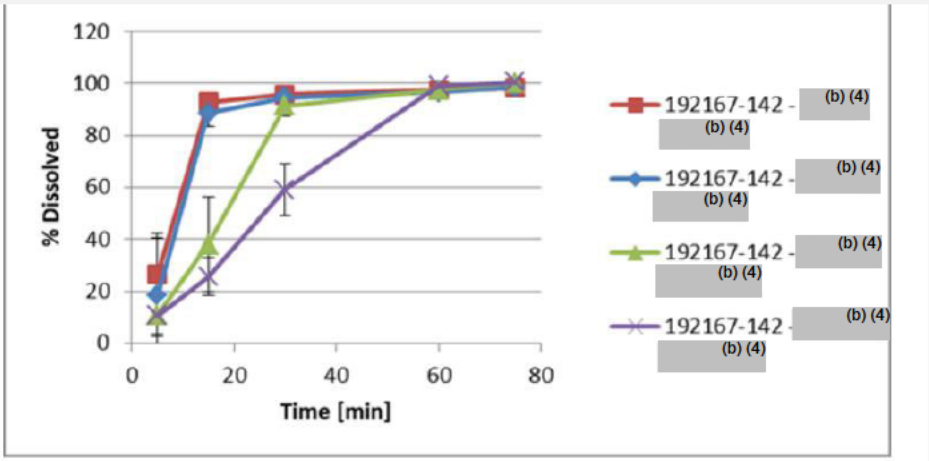


Discriminating Ability of Dissolution Method with Respect to Tablet Hardness

The dissolution method was shown to discriminate dissolution rates due to changes in tablet hardness. The tablets with the higher hardness (b) (4) for 100 mg; Target Range: (b) (4) and (b) (4) for 400 mg; Target Range: (b) (4) resulted in significant decrease in dissolution (**Figures 5** and **6**). Noted that the Applicant has updated the lower control limit for the 100 mg tablet hardness from "Range (b) (4) to "Range (b) (4) as they revised the

dissolution acceptance criterion from (b) (4) minutes to 30 minutes specification time points during review cycle (SDN-43); refer to the Process Review for the adequacy of the tablet hardness control.

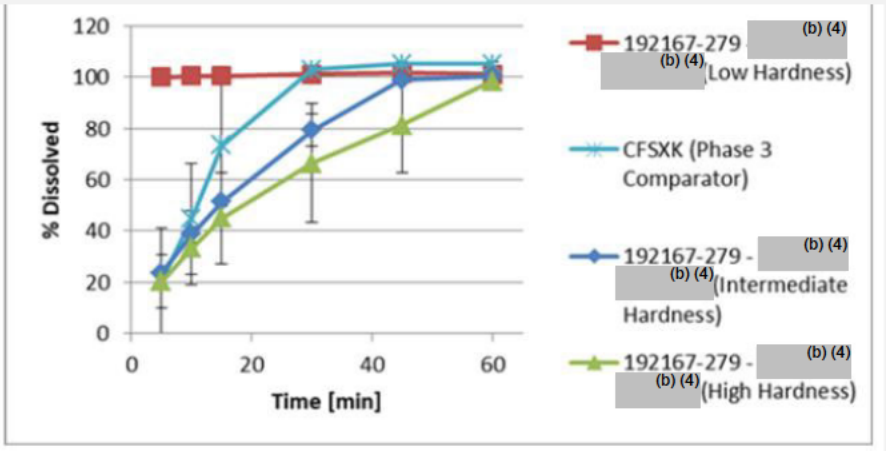
Figure 5: Dissolution Profiles of 100 mg Pre-Registration Batch 192167-142 (Commercial Formulation F) with Increasing (b) (4) Tablet Hardness



Sources: Table 51, Table 52, Table 53, and Table 54

Ref. Figure 9 of 3.2.P.2.2

Figure 6: Dissolution Profiles of 400 mg Pre-Registration Batch 192167-279 (Commercial Formulation F) with Increasing (b) (4) Tablet Hardness



Sources: Table 59, Table 62, Table 60, and Table 61.

Ref. Figure 11 of 3.2.P.2.2

Discriminating Ability of Dissolution Method with Respect to API Particle Size

Based on the PSD data (Table 4 in Section 1.1.3 Module 3.2.P.2) for the API lots that have been manufactured into clinical tablet lots, the PSD values have ranges of (b) (4) um, (b) (4) um, and (b) (4) um for D10, D50, and D90, respectively. The proposed dissolution method has not been shown to be discriminating between the tablets produced with the smallest particle size (D10: (b) (4) um, D50: (b) (4) um, and

D90: (b) (4) µm) and the largest particle size distribution (D10: (b) (4) µm, D50: (b) (4) µm, and D90: (b) (4) µm) drug substance. All the product lots manufactured within the API PSD ranges achieved more than (b) (4) % dissolution at 30 minutes regardless the variabilities at early time points (Figures 1 and 2 in Section 1.1.3 Module 3.2.P.2). The Applicant was recommended to (b) (4) the API PSD based on the mean plus approximately three standard deviations of the PSD data to better reflect the API PSD characteristics used in drug product clinical lots (refer to the Drug Substance Review).

Validation of Dissolution Method: The proposed QC dissolution method has been validated with respect to the analytical HPLC method (refer to the Drug Product Review). The robustness with respect to the dissolution method parameters was demonstrated by varying the concentration of dissolution medium (0.01 N HCl vs (b) (4) N HCl) and paddle speed ((b) (4) vs 75 rpm) for both strengths. The complete dissolution data generated using the proposed dissolution method from the clinical and registration/stability batches demonstrate the repeatability, reproducibility, and robustness of the dissolution of the proposed drug product on a batch-to-batch basis.

Dissolution Acceptance Criterion: The dissolution acceptance criterion of Q= (b) (4) % at (b) (4) minutes proposed by the Applicant was found to be permissive and not acceptable. (b) (4) Response to Information request (SDN-29), the Applicant clarified that the pivotal BE batches were manufactured December 2020 and the clinical trial use spanned from April to July 2021.

In an amendment (SDN-43), the Applicant acknowledged the FDA's recommendation, and revised the dissolution acceptance criterion to "NLT (b) (4) % (Q) at 30 minutes". The Applicant updated Section 3.2.P.5.1 to include the new proposed specification, and Section 3.2.P.5.6 to reflect the justification for the acceptance criterion of NLT (b) (4) % (Q) at 30 minutes. The Applicant's response is adequate.

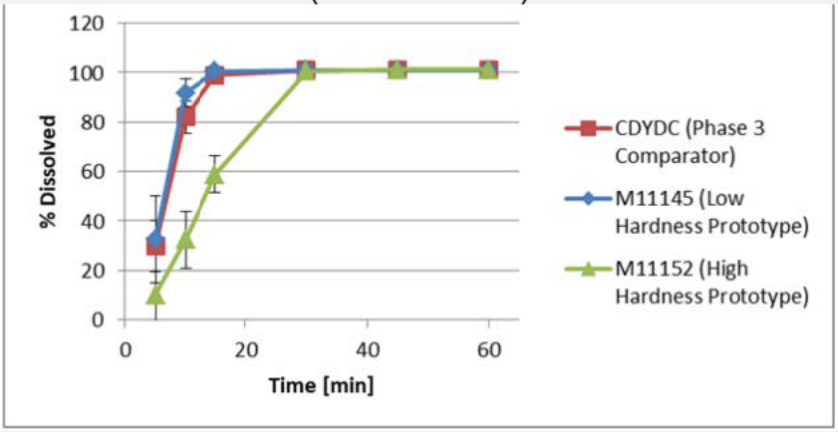
B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: ***Adequate to Support Q= (b) (4) % at 30 minutes***

Data Evaluating the PK of Different Formulation Variants: Two 400 mg commercial formulations with different tablet hardness (**Table 3**) were evaluated (under fasted or fed conditions) and compared to the phase 3 clinical batch (under fed condition) in a Pilot PK study (RAD1901-112). The PK results (AUC, Cmax, Tmax, and T1/2) of the two variant tablets were similar when administered under

fasted and fed conditions and met the criteria for bioequivalence to the phase 3 clinical tablet under fed conditions. The dissolution profiles (**Figure 7**) of the low hardness commercial tablet and phase 3 tablet were dissolved completely within 15 minutes, while the high hardness commercial tablet was completely dissolved at 30 minutes. This indicate that the difference in dissolution before 30 minutes is unlikely to impact in vivo performance because all 3 formulations were shown to produce similar PK results, despite the difference in tablet hardness and the change in formulation.

Figure 7: Dissolution of Elacestrant Tablets, 400 mg, Pilot PK Low and High Hardness Prototypes (Formulation E) and their Phase 3 Comparator (Formulation D)



Ref: Figure 4 of 3.2.P.2.2

Table 3: Hardness of Pilot PK (RAD1901-112) Prototypes (Formulation E, Batches M11145 and M11152) and Phase 3 Comparator (Formulation D; Batch CDYDC) Tablets, 400 mg

Bulk Batch Number	Packed batch	Clinical Label Batch Number	Batch Size	Tablet Hardness
M11145	M11151	M11212	(b) (4)	(b) (4) (low hardness)
M11152	M11162	M11213		(b) (4) (high hardness)
CDYDC	CDYDG	CFKKW[a]	N/A	(b) (4)

[a] Four bottles of CDYDG were labeled as CFKKW for use in RAD1901-112.

Ref: Table 17 of 3.2.P.2.2

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

A list of all the formulations for clinical trials is presented in **Table 4**. The table outlines the changes that were made throughout the development of this drug product and a comparison between early clinical, phase 1 and 3 (Formulation D), pilot PK (Formulation E), and the final commercial formulation (Formulation F). The final commercial drug product (Formulation F) has different formulation and

manufacturing site from the phase 3 tablets. Bridging between the clinical and commercial drug products has been established based on the pivotal clinical BE study [RAD1901-116]. Refer to the OCP Review for the supporting PK data.

Table 4: Formulations Used in Product Development

Formulation	Description	Strength / Dosage Form	Manufacturing Site	Batch Use	Development Initiatives
A	IV formulation	1 mg/mL solution for infusion	(b) (4)	Clinical	Initial
B	Powder in capsule (PIC) formulation	1 mg, 10 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg capsules		Clinical	Initial
C1/C2	Early Clinical prototypes (C1) And Clinical Prototypes (C2)	5 mg, 20 mg and 500 mg (C1) 200 mg 400 mg and 500 mg (C2)		Development	(b) (4)
D	Phase 1 and Phase 3 clinical formulation	100 mg and 400 mg		Clinical (Phase 3) Pilot PK study RAD 1901-112 (as comparator, only 400 mg strength) Pivotal BE study RAD1901-116 (as comparator, both strengths)	
E	Commercial prototype	400 mg	(b) (4)	Pilot PK study RAD 1901-112	(b) (4)
F	Final commercial formulation	100 mg and 400 mg		Pivotal BE study RAD1901-116	

Ref. Table 6 of 3.2.P.2.2

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:
Qi Zhang, Ph.D. (11/10/2022)

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Anitha Govada, Ph.D. (11/10/2022)

Qi Zhang

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Anitha Palamakula Govada

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Date: 11/10/2022 03:33:39PM
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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