

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210326Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

**Recommendation: Approval**

**NDA 210326  
Review #3**

Drug Name/Dosage Form	Injection
Strength	250 mg per 5mL
Route of Administration	Intramuscular
Rx/OTC Dispensed	Rx
Applicant	Fresenius Kabi USA, LLC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA 0001	08/31/2017	API/DP/Process/Microbiology/Facility /CDRH ODE/CDRH OC
Resubmission 0018	02/12/2019	Process/Facility
Resubmission 0023	03/20/2019	Facility
Quality Amendment 0025	04/29/2019	Facility

**Quality Review Team**

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Facility	Feiyan Jin	Daniel Obrzut
Application Technical Lead	Xiao Hong Chen	
RBPM	Kristine Leahy	

**Quality Review Data Sheet**

**1. RELATED/SUPPORTING DOCUMENTS**

N/A

**2. CONSULTS**

N/A

## Executive Summary

### I. Recommendations and Conclusion on Approvability

CMC review for the original NDA 210326 submitted on 3/31/2017 was completed and recommended Approval. Due to the patent status (not expiring) for the listed drug, Faslodex, 250 mg/5mL, NDA 021344, the FDA issued a tentative approval letter to the applicant of this NDA on 6/29/2018. In the previous resubmission (SN 0018) dated 02/12/2019, the CMC information remains unchanged from the original NDA submission except that the applicant added an alternate drug product packaging/labeling site. The acceptability of the new packaging/labeling site has been reviewed by the process/facility reviewer and found acceptable. The product quality review team recommends approval for this NDA. Before the FDA was going to issue an action letter, the applicant submitted a request to withdraw the resubmission (#0018). Five days later on 03/20/2019, the applicant resubmitted the NDA for a Class 1 resubmission. There are no CMC related changes for the resubmission except an editorial correction of a mistake of the FEI number for one of the facilities. The process/facility secondary reviewer, Dr. Daniel Obrzut, stated in the email that the overall recommendation for the manufacturing facilities remain as “Acceptable”. Please refer to the IQA for the resubmission (SN 0018) dated 02/12/2019.

Product Quality review team recommends Approval for the current resubmission.

### II. Summary of Quality Assessments

#### A. Product Overview

<p><b>Proposed Indication(s) including Intended Patient Population</b></p>	<p>Fulvestrant Injection is an estrogen receptor antagonist indicated for the: Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.</p>
<p><b>Duration of Treatment</b></p>	<p>Until disease progression or unacceptable toxicity</p>
<p><b>Maximum Daily Dose</b></p>	<p>Fulvestrant Injection 500 mg should be administered intramuscularly into the buttocks (gluteal area) slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter.</p> <p>A dose of 250 mg is recommended in patients with moderate hepatic impairment to be administered intramuscularly into the buttock (gluteal area) slowly (1</p>

	- 2 minutes) as one 5 mL injection on days 1, 15, 29 and once monthly thereafter.
<ul style="list-style-type: none"><li>• <b>Alternative Methods of Administration</b></li></ul>	N/A

**B. Quality Assessment Overview**

Refer to IQA for the original NDA and resubmission (SN# 0018) dated 2/12/2019.

**C. Special Product Quality Labeling Recommendations (NDA only)**

N/A.

**D. Final Risk Assessment**

Refer to IQA #1

***Application Technical Lead Name and Date:***

Xiao Hong Chen, Ph.D.

30-Apr-2019



Xiao  
Chen

Digitally signed by Xiao Chen

Date: 5/01/2019 10:01:43AM

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**CMC - LABELING**

*NDA 210326  
Fulvestrant Injection  
Fersenius Kabi, LLC*

**I. Package Insert** (amendment SN-010)

**1. Highlights of Prescribing Information**

FULVESTRANT injection, for intramuscular use

-----INDICATIONS AND USAGE-----

Fulvestrant Injection is an estrogen receptor antagonist indicated for the:

- Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. (1)

-----DOSAGE AND ADMINISTRATION-----

- Fulvestrant Injection 500 mg should be administered intramuscularly into the buttocks (gluteal area) slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter. (2.1, 14)
- A dose of 250 mg is recommended in patients with moderate hepatic impairment to be administered intramuscularly into the buttock (gluteal area) slowly (1 - 2 minutes) as one 5 mL injection on days 1, 15, 29 and once monthly thereafter. (2.2, 5.2, 8.6)

-----DOSAGE FORMS AND STRENGTHS -----

Fulvestrant Injection, an injection for intramuscular administration, is supplied as 250 mg/5 mL fulvestrant. (3)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Fulvestrant Injection (no proprietary name)
Dosage form, route of administration	Solution for intramuscular injection into the buttocks
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Fulvestrant Injection, an injection for intramuscular administration, is supplied as 250 mg/5 mL fulvestrant

**2. Section 2 Dosage and Administration**

- 2 DOSAGE AND ADMINISTRATION
- 2.1 Recommended Dose

The recommended dose of Fulvestrant Injection is 500 mg to be administered intramuscularly into the buttocks (gluteal area) slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter [see Clinical Studies (14)].

## 2.2 Dose Modification

### Hepatic Impairment:

A dose of 250 mg is recommended for patients with moderate hepatic impairment (Child-Pugh class B) to be administered intramuscularly into the buttock (gluteal area) slowly (1 - 2 minutes) as one 5 mL injection on days 1, 15, 29 and once monthly thereafter.

Fulvestrant Injection has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) [see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)].

## 2.3 Administration Technique

Administer the injection according to the local guidelines for performing large volume intramuscular injections.

NOTE: Due to the proximity of the underlying sciatic nerve, caution should be taken if administering Fulvestrant Injection at the dorsogluteal injection site [see Warnings and Precautions (5.3) and Adverse Reactions (6.1)].

The proper method of administration of Fulvestrant Injection for intramuscular use is described in the following instructions.

For each syringe:

1. Remove glass syringe barrel from tray and check that it is not damaged.
2. Inspect drug product in glass syringe for any visible particulate matter or discoloration prior to use. Discard if particulate matter or discoloration is present.
3. Peel open the safety needle (SafetyGlide) outer packaging.
4. Hold the syringe upright. Twist and remove the Luer tip cap (see Figure 1).

Figure 1

5. Do Not Touch the Sterile Syringe Tip (Luer-Lok).
6. Attach the safety needle to the syringe tip (Luer-Lok). Twist needle until firmly seated (see Figure 2). Confirm that the needle is locked to the Luer connector before moving or tilting the syringe out of the vertical plane to avoid spillage of syringe contents.

Figure 2

For Administration:

7. Pull needle cap straight off needle to avoid damaging needle point.
8. Expel excess gas from the syringe (a small gas bubble may remain).
9. Administer intramuscularly slowly (1-2 minutes/injection) into the buttock (gluteal area). For user convenience, the needle 'bevel up' position is orientated to the lever arm, as shown in Figure 3.

Figure 3

10. After injection, immediately activate the lever arm to deploy the safety shield by applying a single-finger stroke to the activation assisted lever arm to push the lever arm completely forward. Listen for a click. Confirm that the safety shield has completely covered the needle (see Figure 4).

NOTE: Activate away from self and others.

Figure 4

11. Discard the empty syringe into an approved sharps collector in accordance with applicable regulations and institutional policy.
12. Repeat steps 1 through 11 for second syringe.

**How To Use Fulvestrant Injection**

For the 2 x 5 mL syringe package, the contents of both syringes must be injected to receive the 500 mg recommended dose.

**SAFETYGLIDE INSTRUCTIONS FROM BECTON DICKINSON**

SafetyGlide is a trademark of Becton Dickinson and Company.

**Important Administration Information**

To help avoid HIV (AIDS), HBV (Hepatitis), and other infectious diseases due to accidental needlesticks, contaminated needles should not be recapped or removed, unless there is no alternative or that such action is required by a specific medical procedure. Hands must remain behind the needle at all times during use and disposal. Do not autoclave SafetyGlide Needle before use. Becton Dickinson guarantees the contents of their unopened or undamaged packages to be sterile, non-toxic and non-pyrogenic.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	None

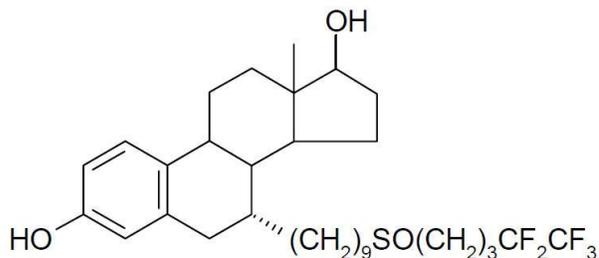
**3. Section 3 Dosage Forms and Strengths**

Fulvestrant Injection, an injection for intramuscular administration, is supplied as 5-mL prefilled syringes containing 250 mg/5 mL fulvestrant.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Solution supplied a 5 mL prefilled syringes
Strengths: in metric system	250 mg/5 mL
Active moiety expression of strength with equivalence statement (if applicable)	250 mg fulvestrant/5 mL (50 mg/mL fulvestrant)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	none

#### 4. Section 11 Description

Fulvestrant Injection for intramuscular administration is an estrogen receptor antagonist. The chemical name is 7-alpha-[9-(4,4,5,5,5-penta fluoropentylsulphonyl) nonyl]estra-1,3,5-(10)- triene-3,17-beta-diol. The molecular formula is C<sub>32</sub>H<sub>47</sub>F<sub>5</sub>O<sub>3</sub>S and its structural formula is:



Fulvestrant is a white powder with a molecular weight of 606.77. The solution for injection is a clear, colorless to yellow, viscous liquid.

Each injection contains (b) (4) **250mg Fulvestrant in a solution composed of 10% w/v (b) (4) Dehydrated Alcohol, USP (b) (4) and 10% w/v Benzyl Alcohol, NF as co-solvents, 0.12% w/v Polysorbate 80, NF as a solubilizing agent, 0.06% w/v Alpha-Tocopherol, USP as a stabilizing agent, and made up to 100% w/v with Castor Oil, USP as a co-solvent and release rate modifier.**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Fulvestrant injection
Dosage form and route of administration	Solution for intramuscular injection into the buttocks
Active moiety expression of strength with equivalence statement (if applicable)	250 mg/5 mL fulvestrant
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	N/A
Statement of being sterile (if applicable)	Sterile
Pharmacological/ therapeutic class	Estrogen receptor antagonist
Chemical name, structural formula, molecular weight	chemical name: 7-alpha-[9-(4,4,5,5,5-penta fluoropentylsulphonyl) nonyl]estra-1,3,5-(10)- triene-3,17-beta-diol molecular formula: C32H47F5O3S structural weight: 606.77
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A

**5. Section 16 How Supplied/Storage and Handling**

Fulvestrant Injection is supplied as two 5 mL clear glass (Type 1) syringes **fitted with a removable tip cap**, each containing 250 mg per 5 mL of Fulvestrant Injection solution for intramuscular use.

**NDC 63323-715-05**

(b) (4)

The pre-filled syringes **with attached plunger rods** are presented in a tray (b) (4) with (b) (4) two **prepackaged** safety needles (SafetyGlide) for connection to the syringes.

Storage:

Store at (b) (4)

**TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE.**

Manufactured for:

Fresenius Kabi [logo]

Lake Zurich, IL 60047

(b) (4)

Made in Austria

451542

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	250 mg/5 mL
Available units (e.g., bottles of 100 tablets)	Single use syringe
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	5 mL clear glass (type I) syringe fitted with a removable tip cap
Special handling (e.g., protect from light)	To protect from light, store in the original carton until time of use.
Storage conditions	(b) (4)
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for Fresenius Kabi, Lake Zurich, IL 60047 Made in Austria, 451542

**Reviewer’s Assessment of Package Insert: *{pending}***

Name & Highlights: No CMC revisions. Established name is acceptable and text is unchanged from reference product package insert.

CMC revisions have been sent to the applicant; response is pending.

Section 2: No CMC revisions. Text provides a clear description of dose administration.

Section 3: No CMC revisions; unchanged from reference product package insert.

Section 11: CMC revisions as indicated to use USP names.

Section 16: CMC revisions made for clarity and completeness.

Section 16 – storage statement: Module 3.2.P.8 includes acceptable stability studies for 2-8°C/30M, 25°C/30M and 40°C/6M. The Faslodex storage statement is

“REFRIGERATE, 2°C-8°C (36°F-46°F). TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE.” The proposed storage statement is “(b) (4) TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE.” The proposed temperature range is (b) (4)

(b) (4). Request that the applicant revise the proposed storage condition statement in the package insert, the syringe label and the carton label to used either the refrigeration {2°C-8°C (36°F-46°F)} or room temperature {20°C-25°C (b) (4)} storage condition statement.

## II. Labels:

### 1. *Syringe Labels* (amendment SN-003)



### 2. *Carton Label* (amendment SN-003)

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

Item	Information provided in the syringe label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Fulvestrant Injection	Fulvestrant Injection
Dosage strength	250 mg/5 mL (50 mg/mL	250 mg/mL (50 mg/mL)
Net contents	5 mL	5 mL
“Rx only” displayed prominently on the main panel	acceptable	acceptable
NDC number (21 CFR 207.35(b)(3)(i))	acceptable	acceptable
Lot number and expiration date (21 CFR 201.17)	acceptable	acceptable
Storage conditions	not sufficient space for the complete statement	not acceptable
Bar code (21CFR 201.25)	acceptable	acceptable
Name of manufacturer/distributor	acceptable	acceptable
And others, if space is available	n/a	n/a

**Reviewer’s Assessment of Labels: {Adequate}**

Established name and strength are correct. See comments and conclusion above regarding the label storage statement.

**List of Deficiencies:**

Package insert CMC revisions as indicated.  
 No CMC revisions for the syringe or carton label.

**Overall Assessment and Recommendation:** Pending

**Primary Labeling Reviewer**

William M. Adams, CMC Reviewer, ONDP/DNDPI 05/16/18

**Secondary Reviewer**

Anamitro Banerjee, Ph.D., Branch Chief, ONDP/DNDPI 05/16/18



William  
Adams

Digitally signed by William Adams  
Date: 5/16/2018 03:14:17PM  
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Anamitro  
Banerjee

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Date: 5/16/2018 07:18:31PM  
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**MICROBIOLOGY****Product Background:**

**NDA:** 210326

**Drug Product Name / Strength:** Fulvestrant Injection, 250 mg/5 ml

**Route of Administration:** Intramuscular (IM) injection

**Applicant Name:** Fresenius Kabi USA, LLC  
Three Corporate Drive  
Lake Zurich, IL 60047  
Telephone: 847-550-2300  
Fax: 847-550-7121

**Manufacturing Site:** Fresenius Kabi Austria GmbH  
Hafnerstrasse 36  
Graz, Austria 8055  
FEI: 3003708554

**Method of Sterilization:** The drug product is [REDACTED] (b) (4)

**Review Recommendation:** Recommended for approval from the standpoint of product quality microbiology.

**Review Summary:** The drug product is supplied as a package of two prefilled 5 ml glass syringes, each containing 250 mg/5 ml of Fulvestrant.

**List Submissions Being Reviewed:** 08/31/2017; 02/12/2018; 03/22/2018; 04/20/2018; 05/04/2018

**Highlight Key Outstanding Issues from Last Cycle:** None

**Remarks:** N/A

**Concise Description Outstanding Issues Remaining:** See the review summary.

**Supporting Documents:**

- The [REDACTED] (b) (4) (ready to use) 5 ml glass syringe barrel, rubber stopper, and plastic rigid tip cover (PRTC) were previously reviewed in 501mic32a1.doc, dated 11/14/2014, and were found to be acceptable.

List Number of Comparability Protocols (ANDA only): N/A

## S Drug Substance

The drug substance, Fulvestrant USP, is supplied by (b) (4). The applicant established specification for the drug substance is  $\leq$  (b) (4) CFU/g for TAMC and  $\leq$  (b) (4) CFU/g TYMC (tested per USP <61>), and  $\leq$  (b) (4) EU/mg for bacterial endotoxins (tested per USP <85>). However, as the drug substance is (b) (4), it will not be reviewed.

### P.1 Description of the Composition of the Drug Product

- Description of drug product** – Fulvestrant Injection, 250 mg/5 ml is a clear and colorless to yellow injectable solution containing 50 mg/ml Desmopressin Acetate in a (b) (4) glass syringe.
- Drug product composition** – The drug product is composed of Fulvestrant, benzyl alcohol, alcohol (b) (4), polysorbate 80, alpha-tocopherol, and castor oil. Additional information regarding the product composition, as derived from Section 3.2.P.1, in the Description and Composition of the Drug Product, is as follows:

Component	mg/syringe	Function	Quality
Fulvestrant	250	API	USP
Benzyl Alcohol	500	Co-solvent	NF
Alcohol (b) (4)	500	Co-solvent	USP
Polysorbate 80	6	Solubilizing agent	NF
Alpha-Tocopherol	3	Stabilizing agent	USP
(b) (4) Castor Oil	Q.S.	Co-solvent and release rate modifier	USP

- Description of container closure system** – Fulvestrant Injection, 250 mg/5 ml is supplied as a pre-filled ready-to-use 5 ml syringe. The syringe assembly (b) (4), rubber stopper (b) (4), secondary enhanced finger flange (b) (4), and plunger rod (b) (4) are all supplied by (b) (4). The syringe assembly includes (b) (4) 5 ml Type I Glass Syringe Barrel and the Plastic Rigid Tip Cap (PRTC) with (b) (4) tip, sealed with a (b) (4) rubber stopper. A summary of the drug product container closure system components is as follows:

Component	Description	Manufacturer/Supplier	DMF # (b) (4)
Syringe Assembly	(b) (4) 5 ml Glass Type I Syringe Barrel, Plastic Rigid Tip Cap (PRTC) (b) (4)		
Plunger Rod	(b) (4) 5 ml Plunger Rod, (b) (4)		
Secondary Enhanced Finger Flange	(b) (4) 5 ml Backstop		
Stopper	(b) (4)		

A representative mock-up image of the drug product was provided:



**Reviewer's Assessment: *Acceptable***

- The description of the drug product composition and container/closure system is adequate.



**Reviewer's Assessment: *Acceptable***

## **P.7 Container Closure**

**Summary table of the container closure system proposed**

**Reviewer's Assessment: See section P.1.**

## **P.8 Stability**

### **P. 8.1 Stability Summary and Conclusion**

The proposed expiry is 30 months.

**Reviewer's Assessment: *Acceptable***

- The applicant's proposed 30 month expiry is acceptable based on the provided endotoxins and microbial test data.

### **P. 8.2 Post-Approval Stability Protocol and Stability Commitment**

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance
Bacterial Endotoxins	USP<85>	NMT (b) (4) EU/mg
Sterility	USP<71>	Sterile

Post-approval stability conditions will be (b) (4). The testing schedule in the post-approval protocol is as follows:

Test Schedule for Initial Commercial Stability Batches									
Long-Term, 25°C ± 5°C/60% ± 5% RH									
Interval (Month)	0	3	6	9	12	18	24	30	36
Bacterial Endotoxins	X	-	-	-	-	-	X	X	X
Sterility	X	-	-	-	-	-	X	X	X
Test Schedule for Annual Commercial Stability Batches									
Long-Term, 25°C ± 5°C/60% ± 5% RH									
Interval (Month)	0	12	24	30	36				
Bacterial Endotoxins	X	X	X	X	X				
Sterility	X	-	X	X	X				

The applicant committed to initiate and conduct post-approval stability studies on the first three commercial production batches, with the results of the testing to be submitted as part of either routine annual reporting or as specified by the Agency, as they become available. If additional data beyond the expiry, on at least three production batches, support extension of the expiration period, the expiration may be extended and the data will be filed in an annual report. If any lot is found to be out-of-specification, the deviation will be discussed with the Agency, and if deemed necessary, the lot will be withdrawn from the market.

**Reviewer’s Assessment: *Acceptable***

- The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product’s microbiological quality throughout its shelf life.

**P.8.3 Stability Data**

The applicant provided bacterial endotoxins and sterility data up to 30 months.

**Reviewer’s Assessment: *Acceptable***

- The applicant provided acceptable microbiology stability data.

## A Appendices

### A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: *Not Applicable*

#### A.2.1 Materials of Biological Origin

Reviewer's Assessment: *Not Applicable*

#### A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: *Not Applicable*

#### A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: *Not Applicable*

### A. 2.4 Viral Clearance Studies

Reviewer's Assessment: *Not Applicable*

## R Regional Information

### *Executed Batch Records*

Executed batches: 16HE0167, 16HB0262, and 16HI0257

The batch records generally confirm that validated (b) (4) manufacturing processes were used for the manufacture of the exhibit batches.

Reviewer's Assessment: *Acceptable*

- The applicant has met the regulatory expectations regarding the executed batch records.

### *Comparability Protocols*

**Reviewer's Assessment: *Not Applicable***

## **2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1**

### **2.A. Package Insert**

Maximum dose: The maximum dose of the drug product is 500 mg administered via two 250 mg/5 ml pre-filled syringes over the course of approximately 4 minutes (1-2 minutes per injection).

Storage: (b) (4)

Description: Fulvestrant Injection, 250 mg/5 ml is supplied as a sterile, clear, and colorless to yellow, viscous liquid for injection in a pre-filled syringe. There is no dilution or reconstitution step.

**Reviewer's Assessment: *Acceptable***

**Post-Approval Commitments: *See P.8.2***

**Reviewer's Assessment: *Not Applicable***

**List of Deficiencies: *N/A***

**Primary Microbiology Reviewer Name and Date:** Jason K. Morgan, Ph.D., 05/07/2018

**Secondary Reviewer Name and Date:** John W. Metcalfe, Ph.D., I concur with the primary reviewer's assessment. 05/10/2018



Jason  
Morgan

Digitally signed by Jason Morgan  
Date: 5/11/2018 07:27:56AM  
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John  
Metcalf

Digitally signed by John Metcalfe  
Date: 5/11/2018 01:47:22PM  
GUID: 503451f000004f68b7145543c615dbba  
Comments: I concur with the primary reviewer's assessment.



## CHAPTER VII: BIOPHARMACEUTICS

**NDA: 210326**

**Drug Product Name / Strength:** Fulvestrant Injection, 250 mg/5 mL

**Route of Administration:** Intramuscular

**Applicant Name:** Fresenius Kabi, USA, LLC (FK USA)

**Background:** Fresenius Kabi, USA, LLC is seeking approval for Fulvestrant Injection, 250 mg/5 mL (50 mg/mL) in a sterile single-use glass prefilled syringe (PFS) intended for intramuscular injection for (1) the treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy, and (2) the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with diseases progression after endocrine therapy *via* the 505 (b) (2) path. The listed drug (LD) is Faslodex® (Fulvestrant) Injection which was approved under NDA 021344 for 250 mg/5 mL (50 mg/mL) strength as a single-use 8 for intramuscular use.

### **REVIEW SUMMARY:**

Because the drug product is a clear and sterile solution for intramuscular injection, in vitro drug release testing is not a requirement for batch release or stability testing of the proposed drug product in the current submission. The Application does not contain biopharmaceutics data that requires assessment. Biopharmaceutics review activity is therefore not necessary for this NDA.

➤ **OVERALL REVIEW RECOMMENDATION:**

- The Division of Biopharmaceutics defers approvability decision making to the other review disciplines.

### **SIGNATURES**

**Primary Biopharmaceutics Reviewer Name and Date:**

Parnali Chatterjee, PhD      10/30/2017

**Secondary Reviewer Name and Date:**

Okpo Eradiri, PhD      10/30/2017



Parnali  
Chatterjee

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Date: 2/05/2018 11:18:00AM  
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Okponanabofa  
Eradiiri

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Date: 2/05/2018 12:01:35PM  
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Attachment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Sterility	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	H	(b) (4)	Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Endotoxin Pyrogen	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	M		Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Assay (API), stability	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	L		Acceptable	Controls are in place, continue stability monitoring post approval
Uniformity of Dose (Fill Volume/deliverable volume)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	L		Acceptable	Controls are in place
Particulate matter (non aggregate for solution only)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	M		Acceptable	Controls are in place. Continue stability monitoring post approval
Leachable extractables	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	L		Acceptable	Absence is demonstrated through the leachable studies performed during development
Appearance (Color/turbidity)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	L		Acceptable	Controls are in place

\*Risk ranking applies to product attribute/CQA

\*\*For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.