CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210326Orig1s000

OTHER REVIEW(S)

MEMORANDUM TO FILE

DATE: April 26, 2019

FROM: Nisha Shah, Senior Regulatory Counsel
Office of Regulatory Policy

TO: NDA 210326 for Fulvestrant Injection, Fresenius Kabi USA, LLC

SUBJECT: Consent Judgment, AstraZeneca Pharmaceuticals LP v. Fresenius Kabi USA, LLC, No. 17-1795 (D. Del. Jan. 22, 2018)

The purpose of this memorandum is to describe FDA's reasoning for determining that approval of NDA 210326 for Fulvestrant Injection submitted by Fresenius Kabi USA, LLC (FK USA) is no longer stayed under section 505(c)(3)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) due to the unexpired patents listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for the relied-upon listed drug, Faslodex (fulvestrant) injection (NDA 021344).

Factual Background

FK USA submitted NDA 210326 on August 31, 2017, pursuant to section 505(b)(2) of the FD&C Act, which relies for approval on Faslodex as a listed drug. AstraZeneca Pharmaceuticals LP (AstraZeneca) is the NDA holder for NDA 021344 for Faslodex. FK USA's application contained paragraph IV certifications to U.S. Patent Nos. 6,774,122, 7,456,160, 8,329,680, and 8,466,139 (Patents) listed in the Orange Book. FK USA provided AstraZeneca notice of the paragraph IV certifications for all the Patents on November 1, 2017, and November 2, 2017. AstraZeneca filed a patent infringement action on December 14, 2017,[1] which triggered a 30-month stay of approval under section 505(c)(3)(C) of the FD&C Act.

On January 22, 2018, the Delaware court entered a consent judgment (Consent Judgment)[2] that provided, in part, that FK USA and AstraZeneca "have agreed to terms and conditions representing a negotiated settlement of the action and have set forth those terms and conditions in a Settlement Agreement (the "Settlement Agreement)." The Consent Judgment further states that:

> 3. Unless otherwise specifically authorized pursuant to the Settlement Agreement, Fresenius, including any of its Affiliates, successors and assigns, is enjoined from infringing the Licensed Patents, on its own part or through any Affiliate, by making, having made, using, selling,

[1] Complaint for Patent Infringement, AstraZeneca Pharmaceuticals LP v. Fresenius Kabi USA, LLC, No. 17-1795 (D. Del. Dec. 14, 2017). AstraZeneca concurrently filed a patent infringement action related to the same patents in the District Court for the District of New Jersey. That New Jersey action was dismissed without prejudice on February 2, 2018. *See* Complaint for Patent Infringement, AstraZeneca Pharmaceuticals LP v. Fresenius Kabi USA, LLC, No. 17-13075 (D. N.J. Dec. 14, 2017) & Order of Dismissal, AstraZeneca v. Fresenius Kabi, No. 17-13075 (D. N.J. Feb. 2, 2018).
[2] Consent Judgment, AstraZeneca v. Fresenius Kabi, No. 17-1795 (D. Del. Jan. 22, 2018).

offering to sell, importing or distributing of the Fresenius Product.

6. All claims, counterclaims, affirmative defenses and demands in these actions are hereby dismissed with prejudice and without costs, disbursements or attorneys' fees to any party.

Discussion

The Consent Judgment does not contain a finding that the Patents are valid, enforceable, or infringed. Also, there is no language in the Consent Judgment enjoining FDA from approving NDA 210326 with respect to the unexpired patents for Faslodex listed in the Orange Book. Therefore, FDA is interpreting the Consent Judgment as a termination of the patent infringement case and a termination of the stay of approval for NDA 210326. This memorandum does not discuss the impact of Faslodex's unexpired exclusivity on the approval of NDA 210326.

Nisha P. Shah -S

Digitally signed by Nisha P. Shah -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nisha P. Shah -S, 0.9.2342.19200300.100.1.1=2001111958
Date: 2019.04.26 11:38:06 -04'00'

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/s/

JEANNETTE L DININ
04/26/2019 12:05:53 PM
uploading for Nisha Shah

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 4, 2018
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 210326
Product Name and Strength:	Fulvestrant Injection, 250 mg/5 mL
Applicant/Sponsor Name:	Fresenius Kabi USA, LLC
FDA Received Date:	June 1, 2018
OSE RCM #:	2018-1805-2
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 1 (DOP1) requested that we review the revised Fulvestrant Injection carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised Fulvestrant Injection carton labeling is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Gao, T. Label and Labeling Review for Fulvestrant Injection (NDA 210326). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 25. RCM No.: 2017-1805-1.

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/s/

TINGTING N GAO
06/04/2018

CHI-MING TU
06/04/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 25, 2018
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 210326
Product Name and Strength:	Fulvestrant Injection, 250 mg/5 mL
Applicant/Sponsor Name:	Fresenius Kabi USA, LLC
FDA Received Date:	May 24, 2018
OSE RCM #:	2017-1805-1
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 1 (DOP1) requested that we review the revised Fulvestrant Injection container label and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label is acceptable from a medication error perspective. However, the revised carton labeling is unacceptable from a medication error perspective. We previously recommended: "Add the statement 'For Administration:' **between** steps 6 and 7 to ensure consistency with Section 2.3 Administration Technique in the proposed Fulvestrant Injection Prescribing Information." However, the Applicant added the statement "For Administration:" to [redacted] (b) (4) steps 8, 9, and 10 are also for administration.

[a] Gao, T. Label and Labeling Review for Fulvestrant Injection (NDA 210326). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 7. RCM No.: 2017-1805.

3 RECOMMENDATIONS FOR FRESENIUS KABI

We recommend the following be implemented prior to approval of this NDA:

A. Carton labeling:

1. As currently presented on the carton labeling, "For Administration:" was added to [redacted] (b) (4). However, our previous recommendation stated: "Add the statement 'For Administration:' **between** steps 6 and 7 to ensure consistency with Section 2.3 Administration Technique in the proposed Fulvestrant Injection Prescribing Information." Therefore, add the statement "For Administration:" **immediately prior to** Step 7 to be consistent with the instructions provided in the proposed Fulvestrant Injection Prescribing Information. See example below:

Section 2.3 Administration Technique in the proposed Fulvestrant Injection Prescribing Information:	**Recommended presentation for carton labeling:**
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. **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. 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.	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. **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.

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/s/

TINGTING N GAO
05/25/2018

CHI-MING TU
05/25/2018

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL, RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Date	May 2, 2018
To	Kristine Leahy; Regulatory Project Manager CDER/OPQ/OPRO/DRBPMI/RBPMBI
Requesting Center/Office	CDER/OHOP /DOPI
OND Review Division	other
From	Sarah Mollo CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Carolyn Dorgan CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for NDA 210326 ICCR2017-01755 ICC1700824
Recommendation	CDRH is recommending that the device constituent of the combination product is approvable for the proposed indication.

Digital Signature Concurrence Table	
Reviewer	Sarah B. Mollo -S Digitally signed by Sarah B. Mollo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sarah B. Mollo -S, 0.9.2342.19200300.100.1.1=2001712033 Date: 2018.05.02 17:38:44 -04'00'
Team Lead	Carolyn C. Dorgan -S Digitally signed by Carolyn C. Dorgan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001800814, cn=Carolyn C. Dorgan -S Date: 2018.05.09 09:05:28 -04'00'
Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9 2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2018.05.11 15:21:31 -04'00'

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2017-01755
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR Forms/Item/displayifs.aspx?List=337aa2e9%2D7692%2D4a76%2Dada9%2Dae967ad4a69b&ID=1982&Web=703664f2%2D33ef%2D4c9f%2Da6f2%2De1f658e187f9
ICC tracking # (Lead)	ICC1700824
Submission Number	NDA 210326
Sponsor	Fresenius Kabi
Drug/Biologic	Fulvestrant Injection 250mg/5ml
Indications for Use	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
Device Constituent	• Two (2), 5mL glass, luer lock-fitted, Pre-Filled Syringes (PFS's) each containing 250mg/5mL (50mg/mL) of drug solution • Two (2), 21G x 1 ½" luer-lock (LL) safety needles
Related Files	n/a

Table 2. Review Team				
Were other disciplines consulted?			☐ **Yes**	☒ **No**
Below is a list of the Discipline Specific ICCR#, ICC# and CON#.				
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**ICCR #**	**ICC #**	**CON #**
n/a				

Table 3. Important Dates	
1st round of Information Requests	01/25/2018
2nd Round of Information Requests	n/a
Final Lead Device Review Memo Due	05/15/2018
Interim Due Dates	**Due Date**
Filing	10/31/2017
74-Day Letter	11/13/17
Mid-Cycle	02/5/18
Primary Review	05/15/2018

PDUFA/GDUFA Due Date	06/30/2018

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2. PURPOSE/BACKGROUND

2.1. Scope

Fresenius Kabi is requesting approval of the Fulvestrant Injection 250mg/5ml PFS. The device constituent of the combination product is a pre-filled syringe.

CDER/OHOP has requested the following consult for review of the device constituent of the combination product on 10/18/2018:

> *Please request a CDRH-OC and CDRH-ODE consult for this combination drug/device product (NDA 210326 - Fulvestrant Injection, 250 mg/5mL prefilled glass syringe).*

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- Device performance
- Biocompatibility of the patient contacting components
- Release Specifications for the device constituent
- Sterility of the device constituent if applicable

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Human Factors

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

2.2. 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.

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.

2.3. Prior Interactions

n/a

2.3.1. Related Files

IND 122336

2.4. Indications for Use

Table 1: Indications for Use

Combination Product	Indications for Use
Fulvestrant Injection 250mg/5ml	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
Pre-filled syringe	Delivery of the drug product
SafetyGlide (safety needle)	K951254; could not locate an indications for use statement in the submission, but the LOA for the 510(k) contains the following intended use: *The BD SafetyGiide™ Needle is used for general purpose injection and aspiration of fluid from vials, ampoules and parts of the body below the surface of the skin. The BD SafetyGiide ™ Needle is compatible for use with standard luer-lock syringes.*

2.5. Dosing and Administration

Fulvestrant 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.

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.

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
Container Closure System (Fulvestrant Injection, 250 mg/5 mL, Prefilled Syringe, Solution for Injection)	Sequence 0001/3.2.P.7 Container Closure System
Stability	Sequence 0001/3.2.P.8 Stability

Combination-Product-Application-Risk-Assessment-AFMEA-Fulvestrant-PFS-425036	Sequence 0002/3.2.P.2 Pharmaceutical Development
Quality Information Amendment (Fulvestrant Injection, 50 mg/mL, PFS)	Sequence 0004/1.11.1 Quality Information Amendment
Quality Information Amendment (Fulvestrant Injection, 50 mg/mL, PFS)	Sequence 0007/1.11.1 Quality Information Amendment
Cover-Letter-17-Apr-2018	Sequence 0008/1.2 Cover Letters

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

Fresenius Kabi USA, LLC's (FK USA) Fulvestrant Injection, 250 mg/5 mL, Solution for Injection will be filled into (b) (4) 5 mL transparent glass syringe with Luer-LokTM adaptor closed with PRTC (b) (4) tip-cap and stoppered with a (b) (4) plunger. Two of the labeled syringes assembled with plunger rods and secondary enhanced finger flange together with two safety needles are packaged in plastic trays with lid (b) (4) in printed folding cartons. Please refer to the below picture which is a representative mock up picture (not of actual size).

Syringe Device Description

Device Characteristic	N/A	Description / Specification
Syringe Name		(b) (4) 5 mL transparent glass syringe with Luer-LokTM adaptor closed with PRTC (b) (4) tip-cap and stoppered with a (b) (4) plunger
Syringe Platform Name (if applicable)		(b) (4) syringe
Priming Dose / Volume		n/a
Drug concentration		250 mg/5 mL
Dose accuracy		NLT (b) (4) mL
Injection Time		Should be administered slowly; 1-2 minutes per injection
Injection Site		buttocks (gluteal area)
Injection tissue and depth of injection		intramuscularly
Audible / visual feedback	n/a	
Cap Removal Force		> (b) (4) N-cm to < (b) (4) N-cm
Breakloose Force		NMT (b) (4) N
Glide Force		NMT (b) (4) N
Visibility of medication container		Glass syringe
Needle Specifications • Length(s) • Gauge(s) • Connection type o ISO 11608-2:2012 o Prestaked		• (b) (4) mm • 21G x 1½ • Luer lock; ISO 594

		The needle length and Gauge is (b) (4) and the connection type is in compliance with ISO 594 and is (b) (4).
Type of Use (e.g. single use, disposable, reusable, other)		Single use
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)		Professional use; The following is included under the patient information in the labeling: *Your healthcare provider will give you Fulvestrant Injection by injection into the muscle of (b) (4) buttock.*
Method of actuation		Press down on plunger
Automated Functions		n/a
Residual Medication		n/a
Drug Container Type		Pre-filled glass syringe
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)		mg; entire dose is delivered for each injection
Environments of use		Clinical setting The following is included under the patient information in the labeling: *Your healthcare provider will give you Fulvestrant Injection by injection into the muscle of (b) (4) buttock.*
Storage conditions and expiry		Store at (b) (4) TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE. (b) (4)
Graduation marks / fill lines		entire dose is delivered for each injection
Preparation and administration (describe all that are applicable) • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc.		<u>Preparation</u> • Remove glass syringe barrel from tray and check that it is not damaged. • Inspect drug product in glass syringe for any visible particulate matter or discoloration prior to use. Discard if particulate matter or discoloration is present. • Peel open the safety needle (SafetyGlideTM) outer packaging. • Hold the syringe upright. Twist and remove the Luer tip cap (see Figure 1). 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.

Safety Features • Needle safety		Safety needle: SafetyGlide
Material composition of PFS		Type I glass syringe

5. DESIGN VERIFICATION AND VALIDATION REVIEW

5.1. Summary of Design V&V Attributes

Table 5: Summary of Design V&V Attributes

Design Verification / Validation Attributes		Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing		x		
To-be-marketed device was used in the pivotal clinical trial?		x		
Selectable dose range on device matches the labeled dose range for the medication?				x
Verification methods relevant to specific use conditions as described in design documents and labeling		x		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)		x		
Traceability demonstrated for specifications to performance data		x		
Conformance to applicable standards demonstrated	ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods			x
	ISO 11608-2:2012 – Needles			x
	ISO 11608-5:2012 – Automated Functions			x
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry		x		
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility	x		
	Sterility			X- not reviewed; syringe is primary container closure

5.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device	x		

Reviewer Comment

An IR was sent to the sponsor to clarify if the to-be marketed syringe was used in the clinical trial. The sponsor confirmed that the proposed commercial syringes were used in the clinical trial as provided in the IND 122336 SEQ-0000.

Syringe	(b) (4) 5 mL Glass Type I Syringe Barrel, Plastic Rigid Tip Cap (PRTC) (b) (4)
Stopper	(b) (4) plunger stopper
Plunger rod	(b) (4) 5 mL Plunger Rod, (b) (4)
(b) (4) **finger flange**	(b) (4) 5mL Backstop
Needle	BD Safety Glide 21G x 11/2"

5.3. Design Verification Review

5.3.1. Design Verification Testing Summary

Essential Functional Requirements						
	N/A	Acceptance Criteria	Method Acceptable	Results/ Deviations	Adequate	
					Yes	No
Dose Accuracy		NLT (b) (4)	yes	Within a/c	x	
Break Loose Force		NMT N	yes	Within a/c	x	
Glide Force		NMT N	yes	Within a/c	x	
Device Requirements						
	N/A	Acceptance Criteria	Method Acceptable	Results/ Deviations	Adequate	
					Yes	No
Needle Connection Type		ISO 594- certification provided of sponsor			x	
Needle Resistance to Bend/Fracture		510(k) cleared- this attribute should not change based on the needle being kitted with a specific drug product			x	
Anti-Needle Stick Performance testing[2]		See reviewer comment below				
Tip cap removal force		> (b) (4) N cm to < (b) (4) N cm	yes	Within a/c	x	

[1]to assess liquid leakage, air ingress, and dye ingress once the syringe is filled with the drug or biological product as intended and when connected to a connecting device. The sensitivity of the selected test method should be specified and validated. System integrity should be demonstrated throughout the product shelf-life.
[2]of an anti-needlestick mechanism with a glass syringe to demonstrate safety and effectiveness as recommended in FDA's guidance document, "Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features " (August 2005).
[3]e.g., needles, adapters, transfer systems, extension tubing, luer connectors, and sharps prevention features
[4]ability of syringe with tip cap to hold a certain pressure on the piston

The following is located under 3.2.P.3.3 Description of Manufacturing Process and Process Controls (Fulvestrant Injection, 250 mg/5 mL Prefilled Syringe, Solution for Injection):

5.3.2. Stability

In compliance with FDA's Guidance to Industry: Q1E Evaluation of Stability Data, effective June 2004, Fresenius Kabi USA, LLC hereby requests an 30-month expiration dating period, at this time, based on the currently available 6 months accelerated (40° C ± 2° C/75% ± 5% RH) and 30 months long-term room temperature (25° C ± 2° C/60% ± 5% RH and 5° C ± 3° C/Ambient RH) stability data.

Table 3.2.P.8.1- 4 Accelerated Stability Test Schedule (Storage Condition: 40°C ± 2°C/75% ± 5% RH)

Test Name	Test Point (months)				
	0	1	2	3	6
Description	H	H	H	H	H
Visual Inspection A. Clarity B. Particulate Matter C. Visual Color	H	H	H	H	H
Volume Check	NP	NP	NP	NP	H
Instrumental Color: YI (D-1925)	H	H	H	H	H
Fulvestrant Assay, Degradation Products, Benzyl Alcohol Assay, and (b) (4)	H	H	H	H	H
(b) (4) Content	H	H	H	H	H
Particulate Matter	H	H	H	H	H
Break loose Force	H	NP	NP	H	H
Gliding(extrusion) Force	H	NP	NP	H	H

H = Horizontal; NP = Not Performed

Table 3.2.P.8.1- 3 Long term Stability Test Schedule (Storage Condition: 25°C ± 2°C/60% ± 5% RH)

Test Name	Test Point (months)										
	0	1	2	3	6	9	12	18	24	27	30
Description	H	H	H	H	H	H	H	H	H	H	H
Visual Inspection A. Clarity B. Particulate Matter C. Visual Color	H	H	H	H	H	H	H	H	H	H	H
Volume Check	NP	NP	NP	NP	NP	NP	NP	NP	H	H	H
Instrumental Color: YI (D-1925)	H	H	H	H	H	H	H	H	H	H	H[D]
Fulvestrant Assay, Degradation Products, Benzyl Alcohol Assay, and (b) (4)	H	H	H	H	H	H	H	H	H	H	H
(b) (4) Content	H	H	H	H	H	H	H	H	H	H	H
Container-Closure Integrity Test	NP	NP	NP	NP	NP	NP	H	NP	H	H[E]	H[C]
Particulate Matter	H	H	H	H	H	H	H	H	H	H	H
Bacterial Endotoxins	H	NP	NP	NP	NP	NP	NP	NP	H	H[E]	H
Break loose Force	H	H	NP	NP	H	NP	H	H	H	H[E]	H
Gliding(extrusion) Force	H	H	NP	NP	H	NP	H	H	H	H[E]	H
Sterility	NP	NP	NP	NP	NP	NP	NP	NP	H[A]	H[B]	H

H = Horizontal; NP = Not Performed;

[A] Added sterility testing for 16HE0167 at 24M;

[B] Added sterility testing at 27M for 16HB0262;

[C] Removed CCIT testing for 16HI0257;

[D] Removed instrumental color at 30M for lot 16HI0257;

[E] Removed testings at 27M for 16HI0257

5.3.3. Environmental Conditioning Testing

The following information is included under shiping-425036:

Summary/Conclusion

The Fulvestrant PFS shipping study was conducted per ASTM D 4169-16 as described in Shipping Plan-Fulvestrant PFS-425036 Version 1.0. Test samples (3 shippers, 80 syringes per shipper; batch P1715019) were filled and assembled in (b) (4) *. They were shipped to outside lab (* (b) (4) *an ISTA certified lab) for shipping test, then visually inspected in* (b) (4) *and evaluated for functional performance.*

Per test results provided in Appendix 1-6, all the Design and Risk requirements defined in the shipping plan (Appendix 7) were satisfied. All the tested samples passed the acceptance criteria by maintaining their integrity, and meeting the performance and labeling legibility requirements.

Test Results

Three (3) shippers went through the simulated shipping per ASTM D4169-16 DC13 (See Appendix 1), which is the US FDA recognized consensus standard for shipping studies. During the shipping study, the shippers underwent simulated shipping conditions including handling, vehicle stacking, loose-load vibration, low pressure, vehicle vibration, and concentrated impact. Per Table 3 of Appendix 1, shipper case was dropped a total of 11 times with drop height of (b) (4) *, then with final drop of double height* (b) (4) **. Shipping provided sample conditioning, e.g. simulated transportation, prior to subsequent visual and functional evaluation.*

<u>Container Closure Integrity Test (CCIT)</u>

Container Closure Integrity Test (CCIT) provides the product sterility information post simulated shipping study. Appendix-3 summarized the Container Closure Integrity Test (CCIT) through Dye Ingress for all three (n=3) shippers. For each shipper, ten (n=10) samples were tested along with 2 positive controls and 2 negative controls. All the test samples passed the acceptance criteria by demonstrating:

1. *None of the samples contains any trace of a blue coloration, while positive control shows a blue coloration.*

2. *The absorbance of UV/Vis (Ultraviolet Visible) of test solution is smaller than or equal to the absorbance of a freshly prepared LOD (Limit of Detection) solution.*

Breakloos/extrusion Force Test

Breakloose/Exrusion(Glide) forces were measured after shipping study to provide additional confirmation that the syringe forces are satisfying the associated Design requirements. Per Appendix-4, six (n=6) samples from each shipper were tested with cross head speed of 100 mm/min. All samples passed the requirements of breakloose force (max=(b) (4) N) not exceeding (b) (4) N and extrusion force (max=(b) (4) N, and min=(b) (4) N) being equal to, or within (b) (4) N and (b) (4) N.

Extractable Volume Test

Extractable volume was evaluated following the shipping study. Appendix-5 summarized the measured PFS extractable volume. Test samples did not pass the extractable volume requirement of greater than, or equal to 5.0ml.

Appendix-6 provided the failure investigation in the Trackwise system (Deviation Event 117242) regarding to this extractable volume Out-Of-Spec (OOS) event. The root cause of the deviation is attributed to a communication error (e.g. Human Error) between (b) (4) and (b) (4), where all the syringes were filled with (b) (4) ml, instead of the requested target fill volume of (b) (4) ml as described in the Shipping Plan-Fulvestrant PFS-425036 Version 1.0. Considering the dead volume of the syringe, the OOS result is expected for those syringes (with initial fill volume of (b) (4) ml when measuring their extractable volume) meeting the acceptance criteria of not less than (b) (4) ml. Therefore, the root- cause of the observed extractable volume being less than (b) (4) ml was due to no enough initial fill volume in the syringe utilized in the shipping study.

Finally, since extractable volume of Sec 4.3.3 is an indirect measurement of container closure integrity, passing the CCIT test in Sec 4.3.1 was a more precise demonstration of the syringe closure integrity being maintained during simulated shipping study (Sec 4.1). It is concluded that the simulated shipping has no impact on the solution volume since the syringe closure system is able to maintain its integrity, e.g. no sign of leakage. Hence, DRM 1.17.1 (extractable volume not less than (b) (4) mL) is satisfied considering all the stability samples per Stability Testing Summary 16HI0257.25H (Volume Check) have already passed the same requirement (DRM 1.17.1).

Reviewer Comment
The sponsors rationale is acceptable.

The failure in fill volume was discussed with CMC via phone. CMC did not have any concerns regarding the failure in the fill volume during the shipping studies, as there are controls in place for fill volume (i.e. release specifications).

4.3.1 Biocompatibility Review

The safety needle is cleared under K951254. The intended use of the cleared 510(k) is not altered through inclusion in the Fulvenstrant PFS kit; therefore, the biocompatibility of the needle should not be re-reviewed for this submission.

Biocompatibility Evaluation		
Materials List	Needle	
Device Characteristics		
Category	☒ External communicating device	
Contact Type	☒ Blood path, indirect ☐ CSF contacting[1] [1]consult biocompatibility consultant	
Contact Duration	☒ ≤24h (limited) • Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), and Material-mediated Pyrogenicity ☐ >24h to 30 days (prolonged) • Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), Material-mediated Pyrogenicity, and Subchronic systemic toxicity ☐ >30 days (permanent) • Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), Material-mediated Pyrogenicity, Subchronic systemic toxicity, and Genotoxicity *Notes:* *The endpoints included in the biocompatibility evaluation of the needle are dependent on the type and duration of contact. Below are the recommended endpoints for blood path, indirect, which are applicable for both subcutaneous and intramuscular injections. If the needle is CSF contacting, information may be needed to support the evaluation of the neurotoxicity endpoint.* ***Repeated use of the device should be considered.*** *This includes cases in which a new syringe a is used each time the drug is administered. For example, if an injection given daily for 1 year would have a total exposure to the needle of ~10 seconds/day for 365 days which equates to ~1 hour.*	

5 RISK ANALYSIS

5.3 Risk Analysis Attributes

Risk Analysis Summary

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	x		
Mitigations are adequate to reduce risk to health	x		

5.4 Summary of Risk Analysis

FK USA employs the use of FMEA (Failure Mode Effects Analysis) to appropriately capture and justify the product's overall risk mitigation strategy and to ensure that identified risks are converted into an appropriate product requirement if required. The various risk assessments were used to generate the product risk requirements, which were subsequently added to the Design Requirement document prior to design verification and design validation.

[…]

In summary, all currently identified risks have been mitigated through the use of Risk Requirements, which have been verified and validated appropriately through verification and validation testing. Per Fresenius Kabi's risk assessment approach, any residual risks with an RPN greater than (b)(4) *require an associated risk/benefit analysis.*

- The sponsor included the following task categories with associated use errors, severity/reasoning, root cause, risk score, and mitigation:
  - Identify Product- Primary and Tertiary Packaging
  - Unpackage Product-Secondary Packaging
  - Inspect Drug/Device
  - Remove Tip Cap
  - Drug Admin-General
  - Inject Drug
  - Drug Storage
  - Syringe Disposal

6 LABELING

Pre-Filled Syringe Labeling Checklist

Attribute		Present		
		Yes	No	N/A
Device Type	Type			
	Syringe Size(s)			
	Needle Gauge			
	Needle Length			
	Quantity			
Prescription Statement under 801.109(b)(1), except for insulin syringes				

Special requirements for insulin syringes as described in 801.403 about mixing insulin, including "For use with U100 insulin only" on the barrel and gradations on the barrel in units;			
Any instructions for using specialized syringes such as the anti-needlestick devices and cartridge syringes;			
Any specific drug or biologic use;			
Instructions on how to clean and sterilize any reusable components.			

6.3 Device Labels

(b) (4)

[redacted]

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

Proposed Labeling

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.

Reviewer Comment
Instructions for use are adequate from CDRH/ODE perspective.

The RPM sent an email on 4/30/18 asking if CDRH has with the labeling change and attached a memo from DMEPA with the following table:

Table 2. Comparative analysis between the comparator Faslodex and the proposed Fulvestrant Injection product

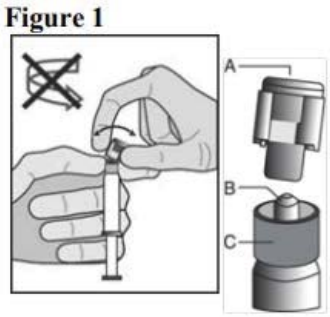
Element	Differences Identified		Applicant's Assessment of the difference	DMEPA's Assessment of the difference
	Faslodex	**Fulvestrant Injection (proposed product)**		
Instructions	Step 1: Remove glass syringe barrel from tray and check that it is not damaged. Step 2: Remove perforated patient record label from syringe. Step: 3: Inspect drug product in glass syringe for any visible particulate matter or discoloration prior to use. Discard if particulate matter or discoloration is present.	Step 1: Remove glass syringe barrel from tray and check that it is not damaged. Step 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.	The Faslodex syringe label has a removable patient record overlay label and a break off Luer Tip Cap which requires 2 steps. The Fulvestrant syringe has a twist off Luer Tip Cap requiring 1 step and no patient record overlay label. The differences in steps results in no usability impact.	Although the proposed Fulvestrant Injection product has no patient record overlay label, this difference will not introduce any new risk of error.
	Step 5: Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully tilt cap back and forth (DO NOT TWIST CAP) until the cap disconnects for removal (see Figure 1). **Figure 1**  	Step 4: Hold the syringe upright. Twist and remove the Luer tip cap (see Figure 1). **Figure 1** 		Our evaluation found the proposed Fulvestrant's different cap and the steps for its removal to be common practice to the healthcare provider end users in the usual clinical setting, and we believe that the different cap and steps will not introduce any new risk. .

Table 2. Comparative analysis between the comparator Faslodex and the proposed Fulvestrant Injection product				
Element	**Differences Identified**		**Applicant's Assessment of the difference**	**DMEPA's Assessment of the difference**
	Faslodex	**Fulvestrant Injection (proposed product)**		
Instructions	For Administration: Step 8: Pull shield straight off needle to avoid damaging needle point. Step 9: Remove needle sheath. Step 10: Expel excess gas from the syringe (a small gas bubble may remain).	For Administration: Step 7: Pull needle cap straight off needle to avoid damaging needle point. Step 8: Expel excess gas from the syringe (a small gas bubble may remain).	The Faslodex syringe refers to the needle shield (Step 8) and Faslodex refers to the needle cap (Step 7). The difference in steps results in no usability impact.	Our evaluation found the proposed Fulvestrant's different cap and the steps for its removal to be common practice to the healthcare provider end users in the usual clinical setting, and we believe that the different cap and steps will not introduce any new risk.
Storage information on carton labeling	Refrigerate, 2°-8°C (36°-46°F). To protect from light, store in the original carton until time of use.	Store at: (b) (4) . To protect from light, store in the original carton until time of use.	No usability impact as Fulvestrant Injection has broader storage conditions than Faslodex. Fulvestrant is not negatively impacted if refrigerated.	Since the proposed Fulvestrant Injection product can be refrigerated, this difference does not introduce any new risk.

Reviewer Comment
CDRH has no concerns with any of the instructions for use.

6.4 Warnings/Precautions/Contraindications

n/a

7 DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The following release specifications are included for the device constituent within eCTD Module 3.2.P.5:

Release Specifications

Attribute	Specification	Test Method
Dose Accuracy	NLT (b) (4) mL	USP <1>
Audible / Visual information on injection status	n/a	n/a
Break Loose/Glide Force	NMT (b) (4) N/ NMT (b) (4) N	(b) (4) - Determination of static and dynamic friction and pull of force of prefilled syringes

Reviewer Comment
Release specifications for the pre-filled syringe are adequate.

8 INTERACTIVE REVIEW

The following IRs were sent on January 25, 2018. The sponsor provided a response on February 12, 2018:

1. Two SafetyGlide Needles are included in the tray as part of the combination product. You have not included the needle specifications within the NDA.

   a. As the needles are part of the combination product, the specifications should be included with the NDA. Please update the NDA to include the specifications for the needle, including but not limited to, the length, gauge, and connection type.

   Sponsor Response
   FK USA acknowledges the agency's question and the ***SPECIFICATION*** *for the BD safety Glide needle is included in the section 3.2.P.7. Additionally, the* ***CERTIFICATE OF COMPLIANCE(COC)*** *from BD is provided with this amendment. The needle length and Gauge is* (b) (4) *and the connection type is in compliance with ISO 594 and is* (b) (4) .

   Reviewer Comment
   The response is adequate. The deficiency is resolved.

   b. If you would like to rely on the 510(k) for the performance testing of the needle, please provide the 510(k) number and the LOA, so that the Agency can review the 510(k) of the needle.

   Reviewer Comment
   The sponsor provided the LOA for K951254. The response is adequate. The deficiency is resolved.

   c. Please confirm that the dose accuracy (i.e. extractable volume), breakloose and glide force were performed using the SafetyGlide needle.

   Sponsor Response

Dose Accuracy/Extractable volume/Volume Check:
The dose accuracy (Extractable volume/Volume check) using safety glide needle is performed as per USP<1> with a limit of NLT (b)(4) mL. The samples used were aged samples from 30ºC and all the samples meet the limit of NLT (b)(4) mL

Break loose and Glide force using safety Glide needle:
The TEST METHOD and REPORT for breakloose and glide force using safety glide needle and aged sample are provided in section 3.2.P.5.2. The Breakloose and Glide force with safety needle has a specification of (b)(4) N and (b)(4) N respectively and the all the results are within specification.

Reviewer Comment
The sponsor has confirmed that the dose accuracy, breakloose force, and glide force verification testing have been performed using the safety glide needle. The response is adequate. The deficiency is resolved.

2. You have referenced the DMF for the (b)(4) 5 mL Glass Type I Syringe Barrel, Plastic Rigid Tip Cap. While it is acceptable to reference the DMF for verification testing, the NDA should include the essential performance requirements, including dose accuracy, breakloose/glide force, and tip cap removal. Please provide the specification for the tip cap removal force for the Plastic Rigid Tip Cap.

Sponsor Response

The specification for the Tip cap removal force using aged samples is > (b)(4) N cm to < (b)(4) N cm
The TEST METHOD and REPORT for the tip cap removal force are provided in section 3.2.P.5.2. All the test results with aged samples are within specification.

Reviewer Comment
The sponsor has provided the tip cap removal force specification and verification testing. The response is adequate. The deficiency is resolved.

3. You have referenced the test method, (b)(4), Determination of static and dynamic friction and pull of force of prefilled syringes; however, the reviewer is unable to locate the results of this testing. Please provide the location of the test results, or the test reports if not previously submitted, for the breakloose and glide force of the combination product (i.e. pre-filled syringe with fulvestrant drug product).

Sponsor Response
*Please refer to section 3.2.P.8.3 Stability data provided in SEQ-0001 for Breakloose (**ACCELERATED** and **LONG TERM CONDITIONS**) and Glide Force (Extrusion Force) (**ACCELERATED** and **LONG TERM CONDITIONS**) using pre-filled syringe with fulvestrant drug product over shelf life.*

Reviewer Comment
The sponsor has referenced the accelerated and long-term stability test results, which include breakloose and glide force at various time-points from 0- 27 months. The results are all within the acceptance criteria. The response is adequate. The deficiency is resolved.

4. You have included a dose accuracy specification (extractable volume) of NLT (b)(4) mL. Please provide the test results for the dose accuracy testing (extractable volume) on the combination product (i.e. pre-filled syringe with fulvestrant drug product).

Sponsor Response
*The Volume check (Extractable Volume) results obtained from the exhibit batches 16HB0262, 16HE0167 and 16HI0257 for both **ACCELERATED** and **LONG TERM** stability data are provided in section 3.2.P.8.3 SEQ-0001 with a specification limit of NLT (b)(4) mL on prefilled syringe with Fulvestrant drug product.*

Reviewer Comment
The sponsor has referenced the accelerated and long-term stability test results, which include dose accuracy at various time-points from 0- 27 months. The results are all within the acceptance criteria. The response is adequate. The deficiency is resolved.

5. The reviewer is unable to location any of the performance testing after shipping (e.g. free-fall, dry-heat/cold storage, damp heat, vibration). Please provide the location of verification of the dose accuracy and breakloose/glide force after stressed conditions that represent those encountered during shipping.

Sponsor Response
*FK USA provides the **SHIPPING STUDY PLAN** and **REPORT** in this amendment. The shipping study was performed to verify the design requirements related to packaging when tested per ASTM D 4169-16 simulated shipping conditions. Extractable volume (dose accuracy), BreakLoose/Extrusion (Glide) Force were evaluated for syringes which experienced the stimulated shipping conditions as per **APPENDIX 4 PAGE 48** and **APPENDIX 5 PAGE 49** of the Shipping Study Report. All samples passed the requirements of Breakloose force (max= (b)(4) N) not exceeding (b)(4) N and extrusion force (max= (b)(4) N, and min= (b)(4) N) being equal to, or within (b)(4) N and (b)(4) N. Extractable volume (Dose accuracy) is an indirect measurement of container closure integrity, passing the CCIT test in **APPENDIX 3 PAGE 45** was a more precise demonstration of the syringe closure integrity being maintained during simulated shipping study. Therefore, it is concluded that the simulated shipping has no impact on the solution volume since the syringe closure system is able to maintain its integrity. Additionally*
*Stability data provided in Section 3.2.P.8.3 has Volume check. The Volume check (Extractable Volume) results obtained from the exhibit batches 16HB0262, 16HE0167 and 16HI0257 for both **ACCELERATED** and **LONG TERM** stability data are provided in section 3.2.P.8.3 SEQ-0001 with a specification limit of NLT (b)(4) mL on prefilled syringe with Fulvestrant drug product.*

Reviewer Comment
The sponsor has provided the requested test plan and data. There was a failure in the extractable volume testing as the fill volume was syringes were filled with (b)(4) ml, instead of the requested target fill volume of (b)(4) ml. Due to the dead volume of the syringe, (b)(4) mL is needed for the syringes to meet an extractable volume acceptance criteria of NLT (b)(4) mL. The sponsor has provided a rationale that since the CCIT passed, for which extractable volume is an indirect measurement, and the extractable volume specification was met during the stability testing, no additional testing is needed. I agree that for the shipping studies, maintenance of the CCIT demonstrates that the shipping conditions will not result in loss of product. The response is adequate. The deficiency is resolved.

Comment to CMC

During the shipping study the extractable volume testing did not meet the specification of NLT (b)(4) mL. The sponsor performed a root cause analysis and determined that the deviation is attributed to a communication error (e.g. Human Error) between (b)(4) and (b)(4), where all the syringes were filled with (b)(4) ml, instead of the requested target fill volume of (b)(4) ml as described in the Shipping Plan-Fulvestrant PFS-425036 Version 1.0. The sponsor has provided adequate information to address the verification testing after shipping; however, I wanted to call attention to the miscommunication regarding the fill volume as it is unclear if the miscommunication is specific to the shipping testing, or in the normal filling process for the to-be marketed product.

Sponsor's Description of event and justification for the acceptability of the results is below:

Extractable volume was evaluated following the shipping study. Appendix-5 summarized the measured PFS extractable volume. Test samples did not pass the extractable volume requirement of greater than, or equal to 5.0ml.

Appendix-6 provided the failure investigation in the Trackwise system (Deviation Event 117242) regarding to this extractable volume Out-Of-Spec (OOS) event. The root cause of the deviation is attributed to a communication error (e.g. Human Error) between (b) (4) and (b) (4), where all the syringes were filled with (b) (4) ml, instead of the requested target fill volume of (b) (4) ml as described in the Shipping Plan-Fulvestrant PFS-425036 Version 1.0. Considering the dead volume of the syringe, the OOS result is expected for those syringes (with initial fill volume of (b) (4) ml when measuring their extractable volume) meeting the acceptance criteria of not less than (b) (4) ml. Therefore, the root- cause of the observed extractable volume being less than 5.0ml was due to no enough initial fill volume in the syringe utilized in the shipping study.

Finally, since extractable volume of Sec 4.3.3 is an indirect measurement of container closure integrity, passing the CCIT test in Sec 4.3.1 was a more precise demonstration of the syringe closure integrity being maintained during simulated shipping study (Sec 4.1). It is concluded that the simulated shipping has no impact on the solution volume since the syringe closure system is able to maintain its integrity, e.g. no sign of leakage. Hence, DRM 1.17.1 (extractable volume not less than (b) (4) mL) is satisfied considering all the stability samples per Stability Testing Summary 16HI0257.25H (Volume Check) have already passed the same requirement (DRM 1.17.1).

6. You have included the accelerated and long term stability test schedule, which includes testing for: break loose force, gliding force, and volume check. Please clarify if volume check can be used to verify dose accuracy of the syringe after aging. The Agency recommends that dose accuracy and breakloose/glide force are verified after stability protocols up to the labeled shelf-life.

Sponsor Response
FK USA confirms that Volume check (Extractable volume) can be used to verify dose accuracy of the syringe with Fulvestrant drug product. The syringes were tested at accelerated and long term conditions and the data is provided in section 3.2.P.8.3 Stability data SEQ-0001 for exhibit batches 16HB0262, 16HE0167 and 16HI0257.

Reviewer Comment
The response is adequate. The deficiency is resolved.

7. Please clarify if the to-be marketed syringe was used in the clinical trial. If not, please describe any differences that could impact the drug delivery (i.e. dose accuracy, leakage, local injection site reactions, etc.).

Sponsor Response
FK USA confirms that the proposed commercial syringes was used in the clinical trial as provided in the IND 122336 SEQ-0000.

Syringe	(b) (4) 5 mL Glass Type I Syringe Barrel, Plastic Rigid Tip Cap (PRTC) (b) (4)
Stopper	(b) (4) plunger stopper
Plunger rod	(b) (4) 5 mL Plunger Rod, (b) (4)
(b) (4) finger flange	(b) (4) 5mL Backstop
Needle	BD Safety Glide 21G x 11/2"

8. Please provide risk analysis information which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states including planned mitigations of these risks, verification of risk mitigations, as well as the acceptability of remaining risks. Your risk analysis should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device. You should outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g. DFMEA, UFMEA, Fault Tree Analysis, etc.).

The following IR was sent on March 28, 2018 The sponsor provided a response on April 2, 2018:

1. You have provided a COC for the Safety glide needle as well as the LOA for K951254. The K951254 does not include a simulated clinical use study for the needle safety device. Additionally, the COC did not contain information verifying the sharps injury prevention feature. The Agency recommends that a clinical use study is performed evaluate sharps injury prevention features. Provide documentation of a clinical use study per FDA guidance document "Guidance for Industry and FDA Staff: Medical devices with Sharps Injury Prevention Features", August 9, 2005. A sample size of 500 with zero failures of the protection feature is recommended. The clinical use study will help FDA evaluate the devices sharps injury preventions feature for its safety and effectiveness. For more information please refer to http://www.fda.gov/medicaldevices/ deviceregulationandguidance/guidancedocuments/ucm071663.htm.

Sponsor Response
*As mentioned in the **Q27** of SEQ-0004, please note that the SafetyGlide™ needle was used in the bioequivalence clinical study with 255 Test and reference subjects. Additionally, the SafetyGlide™ needle which is an off-the-shelf component used from BD (LOA for K951254) in the Fulvestrant Injection is identical to the needle currently marketed by the RLD. Based on the above reasons and guidance: Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA January 2017 section II, which interprets that evaluation between the proposed drug and RLD is required, only, if identical design is not feasible. Since the SafetyGlide™ needle between Fulvestrant Injection (proposed drug) and RLD are identical; FK USA concludes no further evaluation is required for the safety glide needle sharps injury preventions feature for its safety and effectiveness.*

Reviewer Comment
The sponsor states that the SafetyGlide Needle was used in the bioequivalence studies; however, they have not provided any information on if the needle safety feature was assessed.

The following IR was sent April 13, 2018. The sponsor provided a response on April 17, 2018:

1. On March 28, 2018, the Agency requested that you provide a clinical use study per the FDA Guidance document "Guidance for Industry and FDA Staff: Medical devices with Sharps Injury Prevention Features", as K951254 does not include a simulated clinical use study for the needle safety device and the COC provided did not contain information verifying the sharps injury prevention feature. You provided a response on April 2, 2018, stating that the SafetyGlide needle was used in the bioequivalence clinical study with 255 Test and reference subjects. Additionally, you reiterated that the SafetyGlide needle which is an off-the-shelf component used from BD (LOA for K951254). The SafetyGlide needle was cleared prior to the implementation of the guidance and simulated use testing per the guidance is not located within the 510(k).

a. In order to leverage the use of the SafetyGlide Needle in the bioequivalence study, please provide documentation that the function of the needle safety feature was evaluated in the bioequivalence study.

b. Alternatively, provide documentation of a clinical use study per FDA guidance document "Guidance for Industry and FDA Staff: Medical devices with Sharps Injury Prevention Features", August 9, 2005. A sample size of 500 with zero failures of the protection feature is recommended. The clinical use study will help FDA evaluate the devices sharps injury preventions feature for its safety and effectiveness. For more information please refer to http://www.fda.gov/medicaldevices/ device regulation and guidance/ guidance documents/ ucm071663.htm.

Sponsor Response
BD confirms that the simulated use study to evaluate the sharp injury is in the clinical use study documentation in section 8 of the 510K (K951254) submitted on March 15, 1995 and cleared on October 07, 1995.The study incorporated 55 nurses where no needle stick injury was recorded. Further there were no major changes to the SafetyGlide™ needle since 1995 after the clearance of the 510K and no recalls were made for needle stick injuries by BD based on the CDRH medical device recalls for needle safety and effectiveness.

However, (b) (4) has a 510k ((b) (4)) where in section part 9, information regarding the stimulated clinical use trial with 400 devices for the sharp injury prevention feature was provided. Thus, the safety and effectiveness of the SafetyGlide™ needle was evaluated to show that in the activated position the needle cover guards against accidental needle sticks during normal handling and disposal of the used needle/syringe combination. Attached is the LOA (b) (4) with this amendment.

Also FK USA brings to the agency's attention that during the bioequivalence study conducted by FK USA, no needle safety failure issue was reported.

Reviewer Comment
The sponsor has provided a LOA for (b) (4), which included a simulated use trial with 400 devices. The response is adequate. **The deficiency is resolved.**

9 RECOMMENDATION

9.3 Recommendation to CDER/OHOP

CDRH is recommending that the device constituent of the combination product is approvable for the proposed indication.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 10, 2018
To:	Julia Beaver, MD Acting Director **Division of Oncology Products 1 (DOP 1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Lidoshore, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kevin Wright, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	Fulvestrant Injection
Dosage Form and Route:	injection, for intramuscular use
Application Type/Number:	NDA 210326
Applicant:	Fresenius Kabi USA, LLC

1 INTRODUCTION

On August 31, 2017, Fresenius Kabi USA, LLC submitted for the Agency's review a 505 (b)(2) New Drug Application (NDA) 210326 for Fulvestrant Injection. The Reference Listed Drug for this application is FASLODEX (fulvestrant) NDA 021344. The proposed indication for Fulvestrant Injection is for the treatment of:

- hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.
- HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.
- HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP 1) on November 7, 2017 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Fulvestrant Injection.

2 MATERIAL REVIEWED

- Draft Fulvestrant Injection PPI received on August 31, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 3, 2018.
- Draft Fulvestrant Injection Prescribing Information (PI) received on August 31, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 3, 2018.
- Approved FASLODEX (fulvestrant) Injection comparator labeling dated November 14, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

RUTH I LIDOSHORE
05/11/2018

KEVIN WRIGHT
05/11/2018

BARBARA A FULLER
05/11/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 10, 2018

To: Julia Beaver, M.D., Acting Director
Division of Oncology Products (DOP1)

Jeannette Dinin, Regulatory Project Manager, DOP1

William Pierce, PharmD, Associate Director for Labeling, DOP1

From: Kevin Wright, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Brian Tran, PharmD, M.B.A., Team Leader, OPDP

Subject: OPDP Labeling Comments for Fulvestrant Injection, for intramuscular use

BLA: 210326

In response to DOP1's consult request dated November 7, 2017, OPDP has reviewed the proposed product labeling (PI), carton labeling and container label for the original NDA submission for fulvestrant injection for intramuscular use (fulvestrant).

OPDP's review of the proposed labeling is based on the draft PI received by electronic mail from DOP1 (Jeannette Dinin) on May 3, 2018, and we do not have any comments.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 31, 2017, and we do not have any comments.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

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/s/

KEVIN WRIGHT
05/10/2018

USE-RELATED RISK ANSLYSIS AND LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 7, 2018
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 210326
Product Type:	Drug-Device Combination Product
Product Name and Strength:	Fulvestrant Injection, 250 mg/5 mL
Device Constituent:	Pre-filled Syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Fresenius Kabi USA, LLC
Submission Date:	August 31, 2017, October 31, 2017 and December 4, 2017
OSE RCM #:	2017-1805
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD
DMEPA Associate Director:	Quynh Nhu Nguyen, MS

1 REASON FOR REVIEW

As part of this 505(b)(2) NDA 210326 review for Fulvestrant Injection, this review evaluates the proposed Fulvestrant Injection container label, carton labeling, and Prescribing Information (PI) to identify areas of vulnerability that could lead to medication errors in response to a consult request from Division of Oncology Products 1 (DOP1).

The proposed Fulvestrant Injection product is a combination product with Fulvestrant as the active ingredient and a pre-filled syringe device constituent part that is indicated for the treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. The listed drug is Faslodex (Fulvestrant) Injection, NDA 021344.

1.1 REGULATORY HISTORY

On August 31, 2017, Fresenius Kabi USA submitted a comparative analysis[a] that included a labeling comparison, a comparative task analysis, and a physical comparison between the proposed product and the comparator for the purposes of identifying the differences between the user interfaces and risks between the two products.

On October 25, 2017, we sent an Information Request to Fresenius Kabi USA that although their comparative analysis is adequate for their proposed product, they still need to submit comprehensive use-related risk analysis to include a comprehensive and systematic evaluation of all the steps involved in using the proposed product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, and the potential clinical consequences of use errors and task failures.[b]

On October 31, 2017, Fresenius Kabi USA submitted a comprehensive use-related risk analysis[c] which determined that "all currently identified risks associated with the production of the Fulvestrant Injection product have been assessed to be acceptable without mitigations or have had mitigations identified which have reduced the risk to As Low As Possible". Therefore, they consider that the overall risk to be acceptable for this product.[d]

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[a] Fresenius Kabi USA, LLC. Fulvestrant Injection, Design Validation Report. Lake Zurich (IL): Fresenius Kabi USA, LLC. 2017 AUG 18. Available at \\cdsesub1\evsprod\nda210326\0001\m3\32-body-data\32p-drug-prod\fulvestrant-inj\32p2-pharm-dev\combination-prod-treshold-analysis-425036.pdf

[b] Fahnbulleh, F. Personal Communication: NDA 210326 Fulvestrant - Information Request. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 October 25. BLA 210326.

[c] Fresenius Kabi USA, LLC. Fulvestrant Injection, Risk Benefit Analysis. Lake Zurich (IL): Fresenius Kabi USA, LLC. 2017 OCT 27. Available at \\cdsesub1\evsprod\nda210326\0002\m3\32-body-data\32p-drug-prod\fulvestrant-inj\32p2-pharm-dev\comb-prod-risk-benefit-analys.pdf and \\cdsesub1\evsprod\nda210326\0002\m3\32-body-data\32p-drug-prod\fulvestrant-inj\32p2-pharm-dev\comb-prod-afmea.pdf

[d] Fresenius Kabi USA, LLC. Re: NDA 210326 Response to Information Request. Lake Zurich (IL): Fresenius Kabi USA, LLC. 2017 OCT 31. Available at \\cdsesub1\evsprod\nda210326\0002\m1\us\12-cover-letter\cover-letter.pdf

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Use-Related Risk Analysis	C
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 USE-RELATED RISK ANALYSIS

We reviewed the use-related risk analysis for the proposed Fulvestrant Injection and we agree that the use tasks identified and evaluated are comprehensive and appropriate for the use of the proposed product. We also find the Applicant's rationale for their determination of severity and potential harm to the patient and users adequate for each task and potential error.

Fresenius Kabi's proposed Fulvestrant Injection product has a few differences when compared to currently marketed Fulvestrant Injection products, such as the comparator Faslodex. We prepare Table 2 to capture our discussion and evaluation of the differences below.

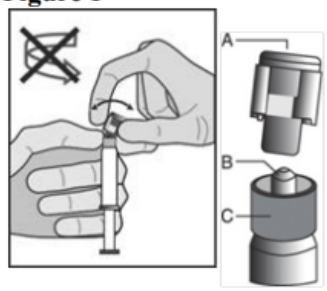
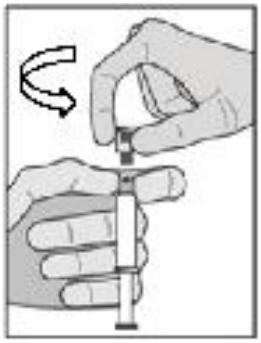
<table>
<tr><th colspan="5">Table 2. Comparative analysis between the comparator Faslodex and the proposed Fulvestrant Injection product</th></tr>
<tr><th rowspan="2">Element</th><th colspan="2">Differences Identified</th><th rowspan="2">Applicant's Assessment of the difference</th><th rowspan="2">DMEPA's Assessment of the difference</th></tr>
<tr><th>Faslodex</th><th>Fulvestrant Injection (proposed product)</th></tr>
<tr><td rowspan="2">Instructions</td><td>Step 1: Remove glass syringe barrel from tray and check that it is not damaged.
Step 2: Remove perforated patient record label from syringe.
Step: 3: Inspect drug product in glass syringe for any visible particulate matter or discoloration prior to use. Discard if particulate matter or discoloration is present.</td><td>Step 1: Remove glass syringe barrel from tray and check that it is not damaged.
Step 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.</td><td rowspan="2">The Faslodex syringe label has a removable patient record overlay label and a break off Luer Tip Cap which requires 2 steps. The Fulvestrant syringe has a twist off Luer Tip Cap requiring 1 step and no patient record overlay label. The differences in steps results in no usability impact.</td><td>Although the proposed Fulvestrant Injection product has no patient record overlay label, this difference will not introduce any new risk of error.</td></tr>
<tr><td>Step 5: Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully tilt cap back and forth (DO NOT TWIST CAP) until the cap disconnects for removal (see Figure 1).
Figure 1
 
</td><td>Step 4: Hold the syringe upright. Twist and remove the Luer tip cap (see Figure 1).
Figure 1
  </td><td>Our evaluation found the proposed Fulvestrant's different cap and the steps for its removal to be common practice to the healthcare provider end users in the usual clinical setting, and we believe that the different cap and steps will not introduce any new risk. .</td></tr>
<tr><td>Instructions</td><td>For Administration:
Step 8: Pull shield straight off needle to avoid damaging needle point.
Step 9: Remove needle sheath.
Step 10: Expel excess gas from the syringe (a small gas bubble may remain).</td><td>For Administration:
Step 7: Pull needle cap straight off needle to avoid damaging needle point.
Step 8: Expel excess gas from the syringe (a small gas bubble may remain).</td><td>The Faslodex syringe refers to the needle shield (Step 8) and Faslodex refers to the needle cap (Step 7).
The difference in steps results in no usability impact.</td><td>Our evaluation found the proposed Fulvestrant's different cap and the steps for its removal to be common practice to the healthcare provider end users in the usual clinical setting, and we believe that the different cap and steps will not introduce any new risk.</td></tr>
</table>

Table 2. Comparative analysis between the comparator Faslodex and the proposed Fulvestrant Injection product				
Element	**Differences Identified**		**Applicant's Assessment of the difference**	**DMEPA's Assessment of the difference**
	Faslodex	**Fulvestrant Injection (proposed product)**		
Storage information on carton labeling	Refrigerate, 2°-8°C (36°-46°F). To protect from light, store in the original carton until time of use.	Store at: (b) (4) . To protect from light, store in the original carton until time of use.	No usability impact as Fulvestrant Injection has broader storage conditions than Faslodex. Fulvestrant is not negatively impacted if refrigerated.	Since the proposed Fulvestrant Injection product can be refrigerated, this difference does not introduce any new risk.

Overall, our evaluation determined that the differences do not introduce any new risk.

3.2 CONTAINER LABEL AND CARTON LABELING

We evaluated the proposed Fulvestrant Injection container label and carton labeling and determined that they could be improved to ensure safe use of the product.

We noted an inconsistency in the use of the package type "Single-Dose pre-filled syringe" on the container label and "For Single-Dose Only" on carton labeling, and defer the determination of the appropriate package type term to the Office of Pharmaceutical Quality (OPQ).

3.3 PRESCRIBING INFORMATION

We reviewed the Dosage and Administration Section, Dosage Forms and Strengths, and How Supplied/Storage and Handling sections of the proposed PI and determined the proposed PI is acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The proposed Fulvestrant Injection PI is acceptable from a medication error perspective. However, the proposed Fulvestrant Injection container label and carton labeling may be improved to ensure safe use of the product. We provide specific recommendations in Section 4.1 below.

4.1 RECOMMENDATIONS FOR FRESENIUS KABI

We recommend the following be implemented prior to approval of this NDA:

A. Container label
    1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, the expiration date format should be presented in accordance with FDA Guidance (e.g. MMMYYYY or MMMDDYYYY).[e]

B. Carton labeling
    1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, the expiration date format should be presented in accordance with FDA Guidance (e.g. MMMYYYY or MMMDDYYYY).[e]
    2. Add the statement "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." Below the statement "INSTRUCTIONS FOR INTRAMUSCULAR USE" to ensure consistency with Section 2.3 Administration Technique in the proposed Fulvestrant Injection Prescribing Information.
    3. Add the statement "For Administration:" between steps 6 and 7 to ensure consistency with Section 2.3 Administration Technique in the proposed Fulvestrant Injection Prescribing Information.

[e] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Fulvestrant Injection that Fresenius Kabi USA submitted on December 4, 2017, and for Faslodex from November 14, 2017 approved Faslodex Prescribing Information[f].

Table 2. Relevant Product Information for Faslodex and Fulvestrant Injection

Product Name	**Faslodex**	**Fulvestrant Injection**
Initial Approval Date	4/25/2002	N/A
Active Ingredient	Fulvestrant	Fulvestrant
Indication	• Treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy. • Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. • Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.	Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.
Route of Administration	Intramuscular	Intramuscular
Dosage Form	Injection	Injection
Strength	250 mg/5 mL	250 mg/5 mL

[f] Faslodex. Drugs@FDA. U.S. Food and Drug Administration; November 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021344s035lbl.pdf.

Table 2. Relevant Product Information for Faslodex and Fulvestrant Injection		
Product Name	**Faslodex**	**Fulvestrant Injection**
Dose and Frequency	Recommended dose: two 5 mL injections, one in each buttock (gluteal area), on days 1, 15, 29 and once monthly thereafter For patients with moderate hepatic impairment: one 5 mL injection on days 1, 15, 29 and once monthly thereafter	
How Supplied	Carton of two 5 mL clear neutral glass (Type 1) barrels in a tray with polystyrene plunger rod and safety needles (SafetyGlide™) for connection to the barrel	Carton of two 5 mL clear glass (Type 1) syringes in a tray with attached plunger rods and two safety needles (SafetyGlide™) for connection to the syringes
Storage	2°-8°C (36°-46°F) Protect from light.	(b) (4) Protect from light.
Container Closure/Device Constituent	The FASLODEX pre-filled syringe (PFS) consists of a (b) (4) glass barrel fitted with a tamper evident closure/luer lock connector, a (b) (4) rubber plunger, (b) (4) rubber tip-cap, a polystyrene plunger rod and a (b) (4) back stop. Secondary packaging for PFS contains two FASLODEX 5 ml PFS presented with two plunger rods in a tray. Each PFS is packed in a carton with closed ends.	(b) (4) 5 mL transparent glass syringe with Luer-Lok adaptor closed with PRTC (b) (4) tip-cap and stoppered with a (b) (4) plunger. Two of the labeled syringes assembled with plunger rods and secondary enhanced finger flange together with two safety needles are packaged in plastic trays with lid (b) (4) in printed folding cartons.
Intended Users	Health care professionals (e.g., physicians and registered nurses)	Health care professionals (e.g., physicians and registered nurses)
Intended Use Environment	Clinical environment	Clinical environment

APPENDIX C. Use-Related Risk Analysis

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following documents submitted by Fresenius Kabi USA.

- Fulvestrant Injection PFS Design Validation Report[h]
- Fulvestrant Injection Risk Benefit Analysis[i]
- Combination Products Application Risk Assessment AFMEA-Fulvestrant PFS-425036[j]

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[h] Fresenius Kabi USA, LLC. Fulvestrant Injection, Design Validation Report. Lake Zurich (IL): Fresenius Kabi USA, LLC. 2017 AUG 18. Available at \\cdsesub1\evsprod\nda210326\0001\m3\32-body-data\32p-drug-prod\fulvestrant-inj\32p2-pharm-dev\combination-prod-treshold-analysis-425036.pdf

[i] Fresenius Kabi USA, LLC. Fulvestrant Injection, Risk Benefit Analysis. Lake Zurich (IL): Fresenius Kabi USA, LLC. 2017 OCT 27. Available at \\cdsesub1\evsprod\nda210326\0002\m3\32-body-data\32p-drug-prod\fulvestrant-inj\32p2-pharm-dev\comb-prod-risk-benefit-analys.pdf

[j] Fresenius Kabi USA, LLC. Combination Products Application Risk Assessment AFMEA-Fulvestrant PFS-425036. Lake Zurich (IL): Fresenius Kabi USA, LLC. 2017 OCT 27. Available at \\cdsesub1\evsprod\nda210326\0002\m3\32-body-data\32p-drug-prod\fulvestrant-inj\32p2-pharm-dev\comb-prod-afmea.pdf

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On December 22, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community
Search Strategy and Terms	Match Exact Word or Phrase: Fulvestrant

D.2 Results

The search retrieved no results.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following Fulvestrant Injection labels and labeling submitted by Fresenius Kabi USA.

- Container label (submitted on August 31, 2017)
- Carton labeling (submitted on August 31, 2017)
- Prescribing Information (Image not shown) (submitted on December 4, 2017)

G.2 Label and Labeling Images

Container label – Prefilled syringe

[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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03/07/2018

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03/07/2018

QUYNHNHU T NGUYEN
03/07/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Abdominal and Surgical Devices Branch

Date:	March 1, 2018
To:	Xiao H. Chen, Ph.D., Chemist, CDER/OPQ/ONDP/DNDPI/NDPBII/ Xiao.Chen@fda.hhs.gov Olen M. Stephens, Chief, CDER/OPQ/ONDP/DNDPI/NDPBII/ Olen.Stephens@fda.hhs.gov Office of Combination Products at Combination@fda.gov **RPM:** Kristine Leahy, Pharm.D., Regulatory Health Project Manager, CDER/OPQ/OPRO/DRBPMI/RBPMBI
Through:	Quality Systems Specialist, CDRH/OC/DMQ

From:	Mary Wen, Ph.D., Biomedical Engineer, CDRH/OC/DMQ/ASDB
Applicant:	Fresenius Kabi USA, LLC Three Corporate Drive Lake Zurich, IL 60047 FEI# 3002733956
Application #	NDA 210326
Consult #	ICC#1700819
Product Name:	Fulvestrant Injection 250 mg/5 ml Pre-Filled Syringe (PFS)
Combination Product Intended Use:	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.
Pre-Approval Inspection:	No
Documentation Review:	No Additional Information Required

Final Recommendation: **APPROVAL (Updated 3/1/2018)**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 210326.

PRODUCT DESCRIPTION

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.

Fresenius Kabi's Fulvestrant Injection product contains 250 mg Fulvestrant, 500 mg Benzyl Alcohol, 500 mg Alcohol (b) (4), 6 mg Polysorbate 80, 3 mg Alphatocopherol, and is brought to quantum satis with (b) (4) Castor Oil.

Fresenius Kabi's Fulvestrant Injection product will be filled into (b) (4) 5 mL transparent glass syringe with Luer-Lok adaptor closed with PRTC (b) (4) tip-cap and stoppered with a (b) (4) plunger (see figure below).

REGULATORY HISTORY

The following facilities were identified as being involved in the manufacturing and/or development of the Fulvestrant Injection 250 mg/5 ml PFS in NDA 210326.

1. Fresenius Kabi Austria GmbH
   Hafnerstrasse 36
   8055 Graz
   Austria
   FEI: 3003708554

   Responsibility – The firm is responsible for manufacturing, in process testing, and finished product testing (including finished product chemistry/analytical testing, sterility and bacterial endotoxin testing, and visual inspection) of the commercial Fulvestrant Injection product.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted 03/29/2016 to 04/01/2016. The inspection covered medical device QS and was classified NAI. Additionally, an inspection that covered drug GMP was conducted 03/98/2017 – 03/17/2017 and was classified VAI.

Inspectional Recommendation – An inspection is **not required** because a recent medical device inspection of the firm was acceptable.

2. Fresenius Kabi USA, LLC
   8045 Lamon Ave Suite 300
   Skokie, IL 60077
   FEI: 3008604776

   Responsibility – The firm is responsible for the design control activities of the Fulvestrant Injection product.

   Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted on 07/20/2017. The inspection covered medical device QS and was classified NAI.

   Inspectional Recommendation – An inspection is **not required** because a recent medical device inspection of the firm was acceptable.

3. Fresenius Kabi Austria GmbH
   Am Gewerbepark 6
   8402 Werndorf
   Austria
   FEI: 3012674433

   Responsibility – The firm is responsible for visual inspection, labeling, secondary packaging, and storage of the commercial Fulvestrant Injection product.

   Inspectional History - An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

   Inspectional Recommendation – An inspection is **not required** because the firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

4. Fresenius Kabi Austria GmbH
   Estermannstrasse 17
   4020 Linz
   Austria
   FEI: 3002807014

Responsibility – The firm is responsible for (b) (4) testing of the finished Fulvestrant Injection product.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted 03/20/2017 to 03/24/2017. The inspection covered drug GMP and was classified VAI.

Inspectional Recommendation – An inspection is **not required** because the firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

5. (b) (4)

Responsibility – The firm serves as an additional site for sterility and bacterial endotoxin testing of the finished Fulvestrant Injection product.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted (b) (4) to (b) (4). The inspection covered drug GMP and was classified NAI.

Inspectional Recommendation – An inspection is **not required** because the firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

6. (b) (4)

Responsibility – The firm is responsible for container/closure integrity testing of the finished Fulvestrant Injection product.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted (b) (4) to (b) (4). The inspection covered drug GMP and was classified NAI.

Inspectional Recommendation – An inspection is **not required** because the firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

7. Fresenius Kabi USA LLC
600 Supreme Drive
Bensenville, IL 60106
FEI: 3007344667

Responsibility – The firm serves as the distribution warehouse for the finished Fulvestrant Injection product.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

Inspection Recommendation:
An inspection is **not required** because the firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part;

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

In Section 3.2.R.4.P.1, the firm provides information regarding management controls for their combination product.

The firm's organizational structure consists of (b) (4) . The firm states that quality requirements are (b) (4) , and that their quality policy is defined in the following (b) (4) :

(b) (4)

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(b) (4)

C. Final Acceptance Activities

In Table 2.3.P-18 on p. 30 – 32 of Section 2.3.P.5, the firm provides a list of finished drug product release specifications, limits, and functional testing:

Test	Acceptance Criteria	Test Method[1]
Description	Liquid in a (b) (4) glass syringe	Visual Examination
Clarity	Clear	USP <1>

Particulate Matter	Essentially free from visible particles	USP <1>
Visual Color	(b) (4)	(b) (4)
Volume Check	NLT(b) (4) mL	USP <1>
Instrumental Color YI (D-1925)	NMT (b) (4)	USP <1061>

Test	Acceptance Criteria	Test Method[1]
A. HPLC	A. The chromatogram of the Low Load Sample Solution exhibits a major peak for Fulvestrant, the retention time of which corresponds to that exhibited in the chromatogram of the Standard Solution and meets the criteria: (b) (4) ≤ Ru/ Rs ≤ (b) (4) Rs : Retention time of Fulvestrant the Standard Solution before the Sample Solution Ru : Retention time of Fulvestrant in the Low Load Sample Solution	(b) (4)
B. UV	B. An extracted UV spectra collected from a photo diode array detector between (b) (4) nm and (b) (4) nm at the apex of the Fulvestrant peak in the Standard Solution and Low Load Sample Solution exhibit maxima at the same wavelength ((b) (4) nm).	

Test	Acceptance Criteria	Test Method[1]
Fulvestrant Assay (Label Claim: 50 mg/mL)	(b) (4) % of Label Claim	(b) (4)
(b) (4)	A. NMT (b) (4) %	(b) (4)
	B. NMT %	
	C. NMT %	

II. Any Unspecified Degradation Product	II. NMT (b) (4)%	
III. Total Degradation Products	III. NMT (b) (4)%	
Benzyl alcohol (Label Claim: 100 mg/mL)	(b) (4) % of Label Claim	(b) (4)
(b) (4)	NMT (b) (4)%	(b) (4)

Test	Acceptance Criteria	Test Method[1]
(b) (4) Content (Label Claim: 100 mg/mL)	(b) (4) % of Label Claim	(b) (4)
Particulate Matter	1. For particles ≥ 10µm, NMT (b) (4) per container	USP <788>[2]
	2. For particles ≥ 25µm, NMT (b) (4) per container	
Sterility	Sterile	USP <71>
Bacterial Endotoxins	NMT (b) (4) EU per mg of Fulvestrant	USP <85>
A. Breakloose Force	A. NMT (b) (4) N	(b) (4)
B. Extrusion (Glide) Force	B. NMT (b) (4) N	
(b) (4)		

Documentation Review Recommendation

This application was deficient. Additional information is required for an adequate documentation review.

Deficiencies to be conveyed to the applicant
The following deficiencies have been identified while doing the documentation review of application Fulvestrant Injection 250 mg/5 ml PFS, NDA 210326, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

1. Your submission does not appear to include information per 21 CFR 820.30, Design Controls. A summary of your firm's design control system under 21 CFR 820.30 must be included for the device constituent part and combination product. The design control information should include initial design, planning and development, design input, design output, design review, design transfer, design verification, design validation that meets the proposed intended use of the final combination product, design changes, and design history file. For changes made to the device constituent part of the combination product, the impact of the design changes on the overall combination product performance should be considered and documented. All the design control activities must be documented in the Design History File (DHF) and subjected for design reviews. In addition, the location of DHF should be provided to the Agency for the facility inspection determination.

2. (b) (4)

3. The description of the manufacturing activities of the finished combination product does not appear to be complete. Although you have provided a description of the in-process and final release testing for the finished combination product, your submission does not appear to clearly specify the acceptance/rejection criteria for receiving components and materials. In order to help us evaluate the applicability of the 21 CFR 820 regulations discussed in 21 CFR Part 4.4(b)(1) to each firm in your submission, please specify your acceptance criteria for receiving components and materials used in the manufacturing of your finished combination product. Please additionally specify which firm conducts each receiving acceptance activity.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for

Industry and FDA Staff,' (2003). This document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

3/1/2018 Update: The above deficiencies were communicated to the firm through via FDA's Information Request dated 2/13/2018; the firm provided a response to the above deficiencies in Section 1.11.1 of SEQ-005 on 2/22/2018. The firm's responses were found to be **adequate.**

RECOMMENDATION

The approvability of application for Fulvestrant Injection 250 mg/5 ml PFS is approvable from the perspective of the applicable Quality System Requirements.

(1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.
(2) The recommended inspections were conducted and deemed acceptable.

Mary Wen, Ph.D.

Prepared: MWen: 03/01/2018
Reviewed:

CTS No.: ICC1700819
NDA 210326

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11/30/2017

TO: Division of Oncology Products (DOP1)
Office of Hermatology and Oncology Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 210326

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Lambda Therapeutic Research, Inc.	460 Comstock Road, Toronto, Ontario, Canada
Clinical	BioPharma Services, Inc.	4000 Weston Road, Toronto, Canada
Clinical	Algorithme Pharma, Inc.	1200 Beaumont Avenue, Mount-Royal, Quebec, Canada
Analytical	(b) (4)	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHILA S NKAH
11/30/2017