

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210063Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

**NDA 210063 Resubmission
Review #2**

Drug Name/Dosage Form	Fulvestrant Injection
Strength	250mg/5ml (50mg/ml)
Route of Administration	Intramuscular
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceuticals USA, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA 0001	12/28/2016	DS/DP/Process/Micro/Biopharm/Facility
Quality Amendment 0012	10/23/2017	Process
Resubmission/Class 2	02/19/2019	DP/Process/Facility
Quality Amendment 0015	03/21/2019	CDRH
Quality Amendment 0020	05/24/2019	CDRH
Quality Amendment 0022	06/05/2019	CDRH
Quality Amendment 0026	07/22/2019	DP

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Substance	N/A	
Drug Product	Amit Mitra	Anamitro Banerjee
Process	Feiyan Jin	Daniel Obrzut
Microbiology	N/A	
Facility	Feiyan Jin	Daniel Obrzut
Biopharmaceutics	N/A	
Device Product	David Wolloscheck	Sarah Mollo
Device Manufacturing	David Wolloscheck	Nikhil Thakur
Regulatory Business Process Manager	Kristine Leahy	

Application Technical Lead (ATL)	Xiao Hong Chen	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

N/A

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA 021344	NDA 021344	Listed Drug, Faslodex

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	Complete	Approval	5/29/2019	David Wolloscheck
CDRH Office of Compliance	Complete	Approval	6/6/2019	David Wolloscheck
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The product quality team in the Office of Product Quality reviewed the resubmission of NDA 210063 after the original NDA received “Complete Response” (CR) letter dated October 26, 2017. The deficiencies in the CR letter were from drug product and process, device characterization (CDRH ODE review for device quality) and manufacturing (CDRH OC review for device manufacturing). The responses to these deficiencies have been reviewed by corresponding disciplines. All deficiencies in the CR letter have been adequately addressed by the applicant and the NDA is recommended for Approval.

II. Summary of Quality Assessments

A. Product Overview

The original 505(b)(2) NDA 210063 submitted on 12/26/2016 seeks approval for Fulvestrant Injection, 250 mg/5 mL (50 mg/mL), that relies on the FDA’s finding of safe and effectiveness of the Listed Drug (LD), Faslodex® (Fulvestrant) injection, NDA 21344. The API and its concentration, the route of the administration (IM), dose and the indications are the same as those of the LD. The only difference between the LD and the proposed drug is the excipients used in the formulation. The original NDA received a Complete Response letter dated 10/26/2017 from the FDA due to the deficiencies in clinical, nonclinical, product quality. The product quality deficiencies are pertaining to the drug product, manufacturing process, as well as deficiencies for device (CDRH) and its manufacturing (CDRH OC). In the current resubmission, the applicant provided complete response to all outstanding product quality deficiencies. The responses have been reviewed by each discipline in the OPQ team as well as CDRH consult team and the deficiencies have been adequately addressed and the NDA is recommended acceptable.

Proposed Indication(s) including Intended Patient Population	Fulvestrant Injection is an estrogen receptor antagonist indicated for the: (b) (4)
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	Recommended dose: • 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.

Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Refer to IQA #1.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment

See Attachment

Application Technical Lead Name and Date:

Xiao Hong Chen, Ph.D.

5-Aug-2019

Attachment

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	(b) (4)	Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place. Continue stability monitoring post approval
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Absence is demonstrated through the leachable studies performed during development
Appearance (Color/turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place

*Risk ranking applies to product attribute/CQA

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



Xiao
Chen

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LABELING

NDA 210063

R Regional Information

1.14 Labeling

1. Package Insert: Is being conducted with the labeling review. ***

(a) “Highlights” Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: N/A Established Name: Fulvestrant Injection	Satisfactory
Dosage form, route of administration	Dosage: 1) Injection Route: Intramuscular	Satisfactory
Controlled drug substance symbol (if applicable)	None	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Fulvestrant injection, for intramuscular use	Not Satisfactory. Strength not included. (b) (4) to “Fulvestrant injection: 250 mg/5 ml” in single-dose prefilled syringe.

Reviewer’s Assessment: Not Satisfactory originally. IR sent: Change from: (b) (4) to “Fulvestrant injection: 250 mg/5 ml in single-dose prefilled syringe”. The changed was noted on the PI. The sponsor accepted the revised PI.

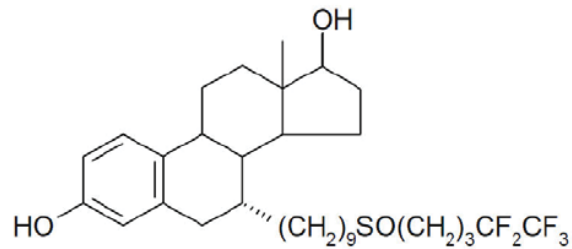
**(b) “Full Prescribing Information” Section
3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Injection	Satisfactory
Strengths: in metric system	250 mg/5 ml	Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Fulvestrant Injection, an injection for intramuscular administration, is supplied as (b) (4) [Redacted] [Redacted]	Change from: “Fulvestrant Injection, an injection for intramuscular administration, is supplied as (b) (4) [Redacted] [Redacted] “Fulvestrant injection, an injection for intramuscular administration is supplied in two 5-mL single-dose pre-filled syringes. Each syringe contains 250 mg fulvestrant/5 mL sterile, clear, colorless to yellow solution”.

Reviewer’s Assessment: Not satisfactory originally. IR sent: Change from: “Fulvestrant Injection, an injection for intramuscular administration, is supplied as (b) (4) [Redacted] to: “Fulvestrant injection, an injection for intramuscular administration is supplied in two 5-mL single-dose pre-filled syringes. Each syringe contains 250 mg fulvestrant/5 mL sterile, clear, colorless to yellow solution”. The revisions were recorded in the PI and they were accepted by the applicant. Adequate.

#11: Description (21CFR 201.57(c)(12))

Fulvestrant Injection for intramuscular administration is an estrogen receptor antagonist. The chemical name is 7- α -[9-(4,4,5,5,5-pentafluoropentylsulphonyl) nonyl]estra-1,3,5-(10)-triene-3,17- β -diol. The molecular formula is $C_{32}H_{47}F_5O_3$ and its structural formula is:



Fulvestrant, USP is a white powder with a molecular weight of 606.77. (b) (4)
(b) (4) The sterile injection solution is a clear, colorless to yellow viscous liquid supplied in two 5 mL single-dose prefilled syringes each containing 250 mg fulvestrant/5 mL for intramuscular administration.

Fulvestrant injection contains the following inactive ingredients in each 5 mL syringe: benzyl alcohol 500 mg (10% w/v) and dehydrated alcohol 500 mg (10% w/v) ^{(b) (4)}; castor oil 3000 mg (60% w/v) ^{(b) (4)} ^{(b) (4)} medium chain triglycerides q.s. to 5 mL (^{(b) (4)}% w/v), and nitrogen q.s.

Reviewer's Assessment: The revised sections in yellow and strikeouts were recorded in the PI and they were accepted by the applicant. Adequate.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary name: N/A Established name: fulvestrant injection	Satisfactory
Dosage form and route of administration	Injection, intramuscular	Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	Strength not included in original label	The PI was requested to be revised to include strength (see above text)
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	See the text above under description section	The PI was requested to be revised to include strength (see above text)
Statement of being sterile (if applicable)	No mention in original PI	The PI was revised to include a statement "sterile".
Pharmacological/ therapeutic class	Estrogen receptor antagonist	Satisfactory
Chemical name, structural formula, molecular weight	Yes	Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Not included	Satisfactory.

Reviewer's Assessment: The PI was revised to include the statements (above). The applicant accepted the revision. Adequate.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Fulvestrant Injection is supplied as two 5 mL clear neutral glass (Type 1) barrels, each containing 250 mg/5 mL of sterile, nonpyrogenic, clear, colorless to yellow Fulvestrant Injection solution for intramuscular injection and fitted with a luer lock connector.

NDC 0591-5019-02

The single-dose prefilled syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlide™) for connection to the barrel.

Storage:

REFRIGERATE, 2°-8°C (36°-46°F). TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE.

The rubber plunger is not made with natural rubber latex.

Sterile, Nonpyrogenic (b) (4)

Handling and Disposal: None included.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	250 mg/5 mL of Fulvestrant Injection solution	Satisfactory
Available units (e.g., bottles of 100 tablets)	Two units	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Fulvestrant Injection is supplied as two 5 mL clear neutral glass (Type 1) barrels, each containing 250 mg/5 mL of Fulvestrant Injection solution for intramuscular injection and fitted with a luer lock connector. NDC 0591-5019-02 The syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlide™) for connection to the barrel.	The identification of dosage form is added to the PI (see yellow highlighted sections)
Special handling (e.g., protect from light, do not freeze)	PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE.	Satisfactory
Storage conditions	REFRIGERATE, 2°-8°C (36°-46°F). TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE	Satisfactory

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributor's name and address included: Made in Italy Manufactured For: Teva Pharmaceuticals USA, Inc. ,North Wales, PA 19454	Satisfactory

Reviewer's Assessment: Revisions highlighted in yellow and strikeouts were included in the PI. The applicant accepted the revision. Adequate.

2. Labels

1) Immediate Container Label

Syringe label



Reviewer's Assessment:

The applicant provided the following required items: Established name, dose strength, route of administration, reference to prescribing information for dosing and administration, prescription only, name and quantity of inactive ingredient, lot #, and expiration date. **Storage condition is not included** (but it is not required). The applicant was recommended to include the storage conditions as follows: **“REFRIGERATE, 2°-8°C (36°-46°F), TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE”**. The applicant agreed to the proposed changes via amendment, dated 19-JUL-2019. See the revised carton label below. Adequate.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name: N/A Established name: Satisfactory	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	None	Satisfactory
Net contents (21 CFR 201.51(a))	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
Storage (not required)	Storage condition not included	The applicant was requested to include the storage conditions. See below.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or	None	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Reviewer's Assessment: IR sent: "REFRIGERATE, 2°-8°C (36°-46°F), TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE". The applicant agreed. See the revised container label. Adequate.

Revised syringe (container) label:



2) Cartons

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Established name: Satisfactory	See immediate container label comment
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	None	Satisfactory
Net contents (21 CFR 201.51(a))	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	None	See comments in the PI.
Sterility Information (if applicable)	Included	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
Storage Conditions	None	Satisfactory

NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling). also see 21	None	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
“See package insert for dosage information” (21 CFR 201.55)	Referenced	Satisfactory
“Keep out of reach of children” (optional for Rx, required for OTC)	None	Satisfactory
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	None	Satisfactory.

Reviewer’s Assessment: The following IR was sent to the applicant based on the review (see above). 1) Revise the statement from: (b) (4)

(b) (4)
 to “Carton contains: A total of 500 mg fulvestrant, in TWO single-dose prefilled syringes each containing 250 mg/5 mL (50 mg/mL), and two SafetyGlide™ shielding intramuscular injection needles. Fulvestrant Injection also contains as inactive ingredients: benzyl alcohol 500 mg (10% w/v), dehydrated alcohol 500 mg (10% w/v), castor oil 3000 mg (60% w/v), medium chain triglycerides q.s. to 5 mL (10.8% w/v), and nitrogen q.s.”; 2) Delete the statement (b) (4)

In an amendment, dated 19-JUL-2019, the applicant agreed. See the revised carton label (attached below). Adequate.

Revised Carton label

(b) (4)

List of Deficiencies: None



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Banerjee

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Amit
Mitra

Digitally signed by Amit Mitra

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OFFICE OF DEVICE EVALUATION

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

**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**



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Date	May 29 th , 2019
To	Mitchell Chan, Program Management, CDER/OND/OHOP/DOPI
Requesting Center/Office	CDER/OHOP
OND Review Division	DOPI
From	David Wolloscheck CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Sarah Mollo CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for NDA 210063 ICCR2019-04529 ICC1900169
Filing Recommendation	Recommendation Date: 3/18/2019 Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Section 11.2
Mid-Cycle Recommendation	Recommendation Date: 5/15/2019 CDRH has Information Requests related to the device constituents parts of the combination product - See Section 11.3 for Information Requests
Final Recommendation	Recommendation Date: 05/29/2019 Device Constituents Parts of the Combination Product are Approvable

Digital Signature Concurrence Table	
Reviewer	
Team Lead	
Branch Chief	

ICC1900169

NDA 210063 , Fulvestrant injection PFS 250 mg/5 mL intramuscular injectable ,

TEVA Pharmaceuticals

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2019-04529
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/Item/displayifs.aspx?List=337aa2e9%2D7692%2D4a76%2Dada9%2De967ad4a69b&ID=4880&Web=703664f2%2D33ef%2D4c9f%2Da6f2%2De1f658e187f9
ICC tracking # (Lead)	ICC1900169
Submission Number	NDA 210063
Sponsor	TEVA Pharmaceuticals
Drug/Biologic	Fulvestrant injection PFS 250 mg/5 mL intramuscular injectable
Indications for Use	Breast Cancer
Device Constituent	Prefilled Syringe
Related Files	ICC1800129

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	03/18/2019
2nd Round of Information Requests	05/21/2019
Final Lead Device Review Memo Due	08/02/2019
Interim Due Dates	
Filing	Due Date
Filing	03/18/2019
Mid-Cycle	5/15/2019
Primary Review	08/02/2019
PDUFA/GDUFA Due Date	08/16/2019

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ICC1900169

NDA 210063 , Fulvestrant injection PFS 250 mg/5 mL intramuscular injectable ,

TEVA Pharmaceuticals

2. PURPOSE/BACKGROUND

2.1. Scope

TEVA Pharmaceuticals is requesting approval of the Fulvestrant injection PFS 250mg/5ml Intramuscular Injectable. The device constituent of the combination product is a prefilled syringe.

CDER/OHOP has requested the following consult for review of the device constituent of the combination product on 02/19/2019:

Intercenter Consult Request (ICCR)

TIER AND CONTACT INFORMATION	
Lead Center: The Center with which the individual submitting the ICCR is affiliated	CDER
Consulted Center: The Center to which the individual receiving the ICCR is affiliated	CDRH
Consult Tier Information: If you have questions on whether an ICCR is Routine ("Tier 2") or Non-Routine ("Tier 3") or appropriate Consulted Center Receivers, contact your Center's Product Jurisdiction Officer: Click to Contact CDER Product Jurisdiction	Routine ("Tier 2") Tier cannot be changed once the ICCR is submitted. If consult tier is incorrect, copy this form to a new ICCR, withdraw this form, and resubmit the new ICCR with corrected tier Other Consult Type Container Closure "Other" Explanation
Lead Center Consult Requester: The individual in the Lead Center who fills out and submits an ICCR form and serves as the contact for the ICCR	Chan, Mitchell Lead Center Requester Office/Division: OND/OHOP/DOPI
Lead Center Submission Contact: The individual in the Lead Center who takes responsibility for the submission or file	Chan, Mitchell
Consulted Center Receiver: identified person or inbox designated to receive ICCRs	CDRH-Combination Product Consults-3 CLICK HERE for a list of contacts in each Center
Others Notified [Optional]: include others to receive e-mail notification that are NOT already identified above.	
Contact Details [Optional] Clarify how contacts above are related to review (e.g., which of above is lead reviewer/PM/ scientific reviewer) or provide other information on review team.	
CONSULTED CENTER ACTION ITEMS	
Assigned Consulted Reviewer(s): Consulted center reviewer who is assigned to complete an ICCR	Wolloscheck, David Assigned Reviewer Office/Division: OHT3
Reviewer Supervisor(s): [Optional]	Stevens, Alan M
Project Manager (PM/RPBM/SRPM): [Optional]	Upadhyaya, Foram *
Consulted Center Tracking Number(s) [Optional] PANORAMA, CTS, or Other Center-Specific Tracking]	ICC1900169
ICCR Draft Review Sent Date [Optional]: [Use to capture interim review sent to lead Center, etc]	Completion Date must be AFTER Draft Review Sent Date SAVE DISABLED - ICCR cannot be saved as DRAFT REVIEW SENT until Sent Date filled above All Required (Red) Fields in Form must also be filled
ICCR Completion Date:	SAVE DISABLED - ICCR cannot be saved as COMPLETED until Completion Date filled above All Required (Red) Fields in Form must also be filled
PRODUCT INFORMATION:	

ICC1900169

NDA 210063 , Fulvestrant injection PFS 250 mg/5 mL intramuscular injectable ,
 TEVA Pharmaceuticals

Product Name	Fulvestrant injection PFS 250 mg/5 mL intramuscular injectable - NDA 210063 505b2	
Applicant/Sponsor:	TEVA Pharmaceuticals	
Indications for Use:	Breast Cancer	
Combo Product Details:	Drug-Device Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc)	
Device Constituent Details:	Device Type: Notes:	Syringe
Drug Constituent Details:	Dosage Form: Notes:	Injection
Biologic Constituent Details:	Biologic Type: Notes:	Other
SUBMISSION INFORMATION:		
Application/Submission Information:	NDA (Other than CMC PAS) Submission Type	210063 Application/Submission Number
Submission Dates:	2/19/2019 Received Date ("Date Stamped" Date)	8/19/2019 FDA Action Date (e.g., MDUFA/PDUFA Goal Date)
Reason for Submission:	Container Closure Submission Notes:	
Other Relevant Submissions: Include Master Files and previous submissions related to review.		
Documentation Location:	Available Electronically	
Documentation Details: Include specific location of information (volumes, pages, or other assistance to reviewer in locating content relevant to ICRR request).	\\CDSESUB1\evsprod\NDA210063\210063 enx	
DESCRIPTION OF THE INTERCENTER CONSULT REQUEST:		
CONSULT DUE DATE:	6/3/2019 If you want to also document intermediate milestones during the review cycle, scroll down to interim milestones/ deliverables Section below.	
Previous/Requested Reviewer(s) [OPTIONAL]:	Mollo, Sarah	
Request Details Provide specific direction to reviewer on scope and output of request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the reviewer. Please review the submission and determine if the appropriate information for device components has been submitted. If not, please determine if the Sponsor needs to submit any further information. Please review prior correspondence regarding this issue as well.		
Lead Center Tracking Number(s): [Optional] PANORAMA, CTS, or Other Center-Specific Tracking #]		
Interim milestones/deliverables, list below with projected dates. Text field only [OPTIONAL]		

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. Prior Interactions

There was a prior CDRH/ODE review conducted for the device constituent parts of NDA 210063 (ICC1700377). The Sponsor failed to respond to the reviewer's information requests during the review cycle and was issued a CR letter.

The following device related deficiencies were issued in the CR letter:

15. The NDA does not include any design requirements and/or specifications for your prefilled syringe. The essential performance requirements should be included within the NDA. This should include, but is not limited to: the expelled volume (accuracy), breakloose force, glide force, and tip cap removal force. You may reference a master file or 510(k) for the actual verification testing (test reports, protocols, etc). However, the expelled volume (dose accuracy), breakloose force, and glide force of the pre-filled syringe should be performed on the combination product including the drug product and the safety needle (i.e., same gauge and length) that is provided with the pre-filled syringe. Provide the design requirements and/or specifications for your prefilled syringe.
16. The table below represents the information needed to complete an adequate review of the device constituents. Provide this information, preferably in tabular format, for each essential performance requirement as specified in your design requirement documentation or provide a justification for why the testing is not necessary. The device requirements should include but are not limited to: deliverable volume (dose accuracy), break loose, glide force, and tip cap removal force.

Essential Performance Requirement	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Dose Accuracy	Ex: No less than 10 mL	{Insert Document Number}	{Insert Document Number or title of completed clinical study}	{Insert Yes if specification was verified after aging the device to the labeled date of expiry}	{Insert Yes if specification was validated after shipping or simulated shipping}	{Insert Yes if specification is a part of the lot release testing of the final finished combination product}
Needle Connection Type	Ex: ISO 11608-2					
Break loose						
Glide force						
Cap Removal Force	Ex: ≤ 15 N					

....						

17. The syringes are presented in a tray with polystyrene plunger rod and SafetyGlide needles. You state that the BD Safety Glide™ Needle, is a Class II, 510(k) Medical Device cleared by the Center Devices and Radiological Health, U.S. FDA CDRH, under 510(k)#: K951254 and that therefore, no letter of access is needed for a 510(k) cleared Medical Device.” However, the needle is being supplied with the syringe and is therefore part of the combination product. The following information regarding the needle was not included within the submission:
- a) Include the design requirements and specifications in the NDA (i.e., length, gauge, connection type, material).
 - b) You may reference a master file or 510(k) for the verification testing; however, for the Agency to review the information within the K951254, you need to submit a letter of authorization (LOA) to review the information within the 510(k) to support the NDA.
 - c) In addition to performance testing per standards addressing the needle requirements (e.g. ISO 7864, ISO 9626, ISO 23908), the 510(k) should include a clinical use study mimics actual clinical use by patient substitutes rather than actual patients and helps evaluate the sharps injury prevention feature. The clinical use study helps to isolate problems with the device, optimize the device design, identify deficiencies in labeling and evaluate the type of training needed for device user. If the 510(k) does not provide a simulated use study, provide documentation of a clinical use study per FDA guidance document “Guidance for Industry and FDA Staff: Medical devices with Sharps Injury Prevention Features,” dated 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>
 - i. [/ucm071663.htm](http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm071663.htm)
 - d) The 510(k) should include a biocompatibility evaluation of the final finished needle component of the pre-filled syringe per the Agency guidance, Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". The endpoints evaluated should be based on the type and duration of contact. As your device is intended to deliver fluids systemically, the Agency recommends that the following endpoints are addressed: cytotoxicity, sensitization, and irritation, acute systemic toxicity, hemolysis, and material-mediated pyrogenicity. If the 510(k) does not evaluate the appropriate endpoints, additional testing may be needed.
18. The release specifications submitted under section 3.2.P.5.1 do not include the breakloose and glide force. These specifications should be included in the release testing for the combination product. Update your release specifications to include the breakloose and glide force.
19. The stability testing does not include the testing of the essential performance requirements of the device constituent of the combination product. Provide stability data supporting the proposed shelf-life of the combination product including testing of the expelled volume (i.e., dose accuracy), breakloose, and glide force of the combination product.
20. The Agency was unable to locate a risk assessment of the combination product. Provide the risk analysis information which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable misuse, and potential system failure states. This should include planned mitigations of these risks, verification of risk mitigations, as well as the acceptability of remaining risks.

21. A description of materials including the material composition (trade name and common name), material supplier, and whether the material is drug and/or patient contacting was not provided. Provide this information and include any additives, processing agents, colorants, etc.

Furthermore, CDRH has issued meeting comments to a type A meeting request on February 22nd, 2018. The following comments were issued regarding the essential performance requirements and the stability testing of the device constituent parts of the product:

Question 16-1:

1. Can the Agency please confirm that the Essential Performance Requirements listed above (Dose Accuracy, Breakloose Force, Glide Force, Tip Cap Unscrewing Torque, CCIT, Needle Safety System Activation Force, Protective Cover Removal Force, and Force Required to Override Safe Mode) constitute the complete list of Essential Performance Requirements for this product that will be required to be tested during lot release testing on the final finished combination product? If not, can the Agency please clarify which additional tests (aside from CMC) will be required?

CDRH Comments

a. You have included the recommended essential performance requirements for pre-filled syringes with needle safety devices, the Agency does not have any recommendations for additional requirements.

b. Including all of the essential performance requirements in the release testing is an acceptable approach; however, for pre-filled syringes dose accuracy, breakloose force, glide force, and container closure integrity are usually considered adequate for device specific release testing for pre-filled syringes.

Question 16-2:

2. Can the Agency please confirm that the above approach to address release, stability and simulated shipping verification data is acceptable?

If the above proposal is not acceptable, can the Agency please confirm that a postapproval commitment to provide t=0 results from the first commercial batch in addition to the above proposal would be considered acceptable? (Teva would also commit to place that first commercial batch on accelerated and real-time stability for the parameters listed above and provide results to the Agency in the Annual Reports as data becomes available.)

CDRH Comments

You state that Breakloose Force, Glide Force, Tip Cap Unscrewing Torque, Needle Safety System Activation Force, Protective Cover Removing Force and Force Required to Override Safe Mode were not included in the stability protocol previously submitted; however, the you intend to perform testing on these parameters just over 24 months (the proposed shelf-life). It is unclear if you plan to complete this testing prior to re-submitting the NDA. The following should be included in the NDA for stability testing:

- Test protocols and test results for the verification of essential performance requirements after accelerated aging representative of the proposed labeled shelf-life
- Test protocols and test results of the verification testing that has been completed after real-time aging protocols at the time of NDA submission (e.g. 6 months)
- the protocol for the planned 24 months of real-time aging studies

Question 17:

Does the Agency agree with Teva's proposal as outlined above?

Sponsor Background

The 510(k) for BD Safety Glide™ Needle (K951254) was originally filed before the “Guidance for Industry and FDA Staff: Medical devices with Sharps Injury Prevention Features,” dated August 9, 2005 was issued. FDA has requested that if the 510(k) does not provide a simulated use study, documentation of a clinical use study per said guidance needs to be provided.

Teva proposes to justify not performing a Simulated Clinical Use study in accordance with the FDA Guidance Document for Medical Devices with Sharps Injury Prevention Features for the off-the-shelf, 510(k) approved BD Safety Glide™ Needles co-packaged with the Fulvestrant Pre- Filled Syringe combination product. The BD Safety Glide™ Needle system has been in use for over 20 years. Hundreds of millions of these systems are sold every year for a variety of medical procedures, from vaccinations to surgical interventions. As such, there have been an extremely large number of procedures performed with the device over this time period, conservatively estimated at 1 billion (50 million procedures per year over 20 years).

The proposed approach will be to conduct a comprehensive vigilance database (for example MAUDE) and literature search of the post-market history of this device and similar active needle safety devices within the US market with a focus on highlighting all use related events when used in Pre-Filled Syringe combination products. All literature and data searches will be documented and included within a summary report, also considering the usability requirements are based on the Annex C of the IEC 62366:2015.

CDRH Comments

The proposed approach is acceptable; however, the Agency recommends that you focus the search specifically on the device that will be included with the combination product (i.e. BD Safety Glide™ Needle, cleared under K951254). Additionally, provide an estimated number of units sold/used as well the number of needle stick injuries from your database/MAUDE and literature search.

2.2.1. Related Files

ICC1700377

ICC1800129

2.3. Indications for Use

Table 1: Indications for Use

Combination Product	Indications for Use
Fulvestrant injection PFS 250 mg/5 mL intramuscular injectable	Treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.
Two (2) prefilled syringes	Delivery of the drug product

3. ADMINISTRATIVE**3.1. Documents Reviewed**

Document Title	Location
Container Closure Summary	GSR 0014/ 3.2.P.7
Teva Response to FDA CR	GSR 0014/ 1.2

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

Is the syringe part of a kit?

The following information was taken from Container Closure Summary and the instructions for use under 3.2.P.7 and 1.14. in GSR.

Syringe Device Description

Device Characteristic	N/A	Description / Specification
Syringe Name		(b) (4)
Syringe Platform Name (if applicable)		(b) (4)
Priming Dose / Volume		5 ml
Dose accuracy		(b) (4)
Injection Time	X	
Injection Site		Buttocks
Injection tissue and depth of injection		Intramuscular
Audible / visual feedback	X	
Cap Removal Force		0.03 to 0.18 Nm
Activation Force	X	
Visibility of medication container		Clear Glass Barrel
Needle Specifications • Length(s) • Gauge(s) • Connection type ○ ISO 11608-2:2012 ○ Prestaked		BD SafetyGlide (K951254) 21G x 1 1/2" RB TW LOA provided
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
Method of actuation		Manual
Automated Functions	X	
Residual Medication	X	

Drug Container Type	X	
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	X	
Environments of use		Healthcare facility
Storage conditions and expiry		24 months shelf-life; Store at 5°C ± 3°C
Graduation marks / fill lines	X	
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.		- Remove needle cap by twisting - Attach BD SafetyGlide needle to the syringe - Pull needle shield straight off - Expel excess gas from syringe - Administer intramuscularly slowly (over 1 to 2 minutes/injection) into the buttock.
Safety Features Needle safety		Needle safety feature of BD SafteyGlide (K951254). Sponsor has provided LoA for the 510(k) in GSR 0014/ 1.4.2.
Material composition of PFS		Syringe: (b) (4) colorless Type I glass Rubber plunger: (b) (4) grey plunger (b) (4) Plunger Rod: Polystyrene Backstop: (b) (4)

Figure 1: Illustration of pre-filled syringe

(b) (4)

The device constituent part of the combination product is a prefilled syringe. The syringe is operated by pushing or pulling on the plunger to inject or withdraw fluids.

Device Description Stock IR

Device Description Recommendation	
The Sponsor Provided Complete Device Description for the Device Constituent	☒
The Sponsor DID NOT Provide Complete Device Description for the Device Constituent	☐
Device Description Information Requests	Section 11.1 Filing IRs - # Section 11.2 74-Day Letter IRs - # Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #
All Information Requests were Resolved over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

5. FILING REVIEW

CDRH performed Filing Review	☒
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

Table 4: Design Control Documentation Check

Design Control Requirement	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		Sponsor’s response to CR letter GSR 1.2
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		Sponsor’s response to CR letter GSR 1.2
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		GSR 3.2.R

Master File Review Instructions

Master File Stock IR

Design Controls Recommendation	
The Sponsor Provided Complete Design Controls for the Device Constituent	☒
The Sponsor DID NOT Provide Complete Design Controls for the Device Constituent	☐
Design Control Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #
All Information Requests were Resolved over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. 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

Referenced Standards and Guidance Documents

Reference Standard / Guidance	Description / Extent of FDA Recognition	Documentation Adequate	
		Yes	No
USP <697>	Recognized in FDA guidance	X	
ISO 11608-1	Complete Standard	X	
ISO 23908:2011	Complete Standard	X	

6.2. Design Validation Review

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

The following three clinical studies were conducted with the combination product:

- This study was conducted to assess the bioequivalence of Fulvestrant from test formulation of Fulvestrant injection 50 mg/mL administered as 5 mL injection compared to that of reference product Faslodex® (Fulvestrant injection 50 mg/mL) administered as 5 mL injection in healthy, adult, human female subjects when administered under fasting conditions. To assess the safety and tolerability of the test formulation and reference product in healthy, adult, human subjects.
- To assess the relative bioavailabilities of Fulvestrant from test formulation of Fulvestrant injection 50 mg/mL administered with different injection volume of 2.5 mL, 3 mL and 3.5 mL compared to that of reference product Faslodex® (Fulvestrant injection 50 mg/mL) administered as 5 mL in healthy, adult, human subjects. To assess the safety and tolerability of the test formulation and reference product in healthy, adult, human subjects.
- This study assessed the relative bioavailability of two test formulations Fulvestrant injection 50 mg/mL, compared to that of Faslodex® (fulvestrant injection 50 mg/mL), in healthy, adult human subjects under fasting condition. To assess the safety and tolerability of the test and reference products in healthy human, adult subjects.

Comparison of TEVA product to approved Faslodex

The Sponsor established design requirements for the subject device by product characterization of the listed combination product Faslodex (LD). The following comparison of the device design requirements was provided by the Sponsor:

Table 7: Teva Combination Product Design requirements and LD comparison

Combination product functionality Essential Performance requirements	Teva's Proposed Specification	Faslodex® (LD)	Teva's Proposed Combination Product (2 year aged)	Teva's Proposed Combination Product (4 year aged)
Dose Accuracy (expelled volume) ¹	(b) (4)			
Break Loose Force				
Dynamic Glide Force				

¹ Dose accuracy or expelled volume testing has been performed to USP<697> Container content for injections or equivalent. The term 'Container Content' maybe used as an equivalent test method name.

Table 9: SafetyGlide™ needle Design requirements and LD comparison

	Teva's Proposed Specification	Faslodex® (LD)	Teva's Proposed Combination Product (2 year aged)	Teva's Proposed Combination Product (4 year aged)
Protective cover removal force	(b) (4)			
Needle safety system activation force				
Force required to override safety mode				
Tip cap opening torque				

In addition to the above comparison to a listed combination product, TEVA has also provided a table of the device design validation activities:

ID#	User Needs	Validation Method	How the evidence validates the user need

U01	A product which does not require additional training.	Technical review and comparative analysis	PASS - A Technical review and comparative analysis performed on Prescribing Information Leaflet demonstrated that instructions show the correct sequence of actions to be followed in order to use of the pre- filled syringe and confirms equivalent to the LD.
U02	A product that can be stored at refrigerated conditions 2°-8°C (36°-46°F) and protected from light.	Technical assessment of the Stability studies and Secondary pack design	PASS - A Technical Review of Stability studies provide objective evidence of suitability of temperature range for storage. Also, Secondary packaging is suitable to protect the product from light.
U03	Operational steps similar to that of LD to administer product.	Comparative analysis with LD	PASS - Comparative analysis conforms that the operational steps to administer product are similar to that of LD.
U04	Combination product shall be used by Health professionals in Hospital or private health care facilities.	Technical review of the Prescribing Information Leaflet.	PASS - A Technical review Prescribing Information Leaflet confirms that the product is for Health professionals in Hospital or private health care facilities
U05	A product that has a shelf life that enables storage before use.	Technical review of the results of Stability studies	PASS - Technical review of Stability Study reports provide confirmation of the proposed shelf life of no less than 24 months; therefore, the combination product has a shelf life that enables storage before use.
U06	A product that is safe to use.	Technical of Human Factors Summary Report	PASS - The Human Factors Summary report concludes that the Fulvestrant Pre-Filled Syringe (PFS) has been found to be safe and effective for the intended users, for its intended use within the intended use environment.
U07	A product that is undamaged at point of use.	Technical Review of Distribution studies	PASS - Technical Review of the results of Distribution Testing provided evidence supporting the ability of the combination product to be supplied undamaged at the point of use.
U08	A product that is identifiable.	Technical review of the carton and instructions	PASS - Technical Review providing confirmation of fulfilment of this requirement is provided by the presence of the tradename of Fulvestrant combination product on device, leaflets and carton
U09	The product can be operated with one hand.	Technical review and Comparative analysis	PASS - Technical review of the Prescribing Information Leaflet has demonstrated the correct sequence of actions to be followed in order to inject and activate the safety system of the SafetyGlide™ needle with one hand.

U10	The device has a Safe mode signal.	Technical review of combination product components and Comparative analysis	PASS - Technical Review of the BD SafetyGlide™ needle demonstrates that the lever arm covers the needle, when activated. Comparative analysis conforms that the safe mode signal (i.e. lever arm covering the needle when activated) is similar to that of LD with no difference identified.
U11	A product that is transportable.	Technical Review of Distribution studies	PASS - Technical Review of the results of Distribution Testing provided evidence supporting the ability of the combination product to be transported to the point of use.
U12	A product that is useable.	Comparative Analysis	PASS - Comparative analysis conforms that the operational steps to administer product are similar to the LD and are not expected to introduce new use errors during normal use or foreseeable misuse scenarios.
U13	A product that has available and understandable information.	Comparative analysis	PASS - Results of the Comparative analysis show that the LD and Teva product IFU and PIL have only minor, permissible differences. The labeling is not expected to introduce new use errors during normal use or foreseeable misuse scenarios.
U15	A product that can be disposed of safely, in accordance with state / local waste regulations and via hospital waste management systems.	Technical assessment of Prescribing Information Leaflet	PASS - Technical review of the Prescribing Information Leaflet for Teva Fulvestrant Injection combination product has been conducted in order to confirm that evidence on presence of information concerning safe disposal of the combination product.

Reviewer Comment:

The Sponsor has conducted clinical studies with the subject device to assess the bioequivalence and bioavailability of Fulvestrant when compared to the listed combination product Faslodex. Furthermore, TEVA has conducted testing to compare the essential performance requirements of Faslodex to the subject device. The provided data showed that EPRs like dose accuracy and breakloose / glide force are similar between the two pre-filled syringes. The expelled volume of Faslodex was (b) (4) mL, whereas for TEVA’s proposed presentation was (b) (4) mL. Both devices meet the requirements of USP <1> and are within the specifications set by TEVA. Break Loose and glide forces were also similar with (b) (4) N (break loose force) and (b) (4) N (glide force) for the LD and (b) (4) N and (b) (4) N for TEVA’s pre-filled syringe. In addition, TEVA has provided a design validation table summarizing design inputs and the validation methods. Overall, the device design validation activities are acceptable.

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Design Validation Recommendation	
The Sponsor Provided Complete Design Validation for the Device Constituent	☒
The Sponsor DID NOT Provide Complete Design Validation for the Device Constituent	☐
Design Validation Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #
All Information Requests were Resolved over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

6.3. Design Verification Review

6.3.1. Design Verification Testing Summary

Essential Functional Requirements						
	N/A	Acceptance Criteria	Method Acceptable	Results/ Deviations	Adequate	
					Yes	No
Dose Accuracy		(b) (4) mL	USP <697> and ISO 11608-1:2014	Results were reported to be 5.07 – 5.14 mL with a sample size of 60	X	
Break Loose Force		NMT (b) (4) N	ISO 11040-4 Annex E	Reported results: 7 – 13 N; Sample size: 60	X	
Glide Force		NMT (b) (4) N	ISO 11040-4 Annex E	Reported results: 27 – 37 N; Sample size: 60	X	
Visual/Audible Feedback	X					
Device Requirements						
	N/A	Acceptance Criteria	Method Acceptable	Results/ Deviations	Adequate	
					Yes	No
Injection Depth	X					
Injection time	X					
Needle Connection Type	X					
Needle Resistance to Bend/Fracture	X					
Seal Integrity Testing ¹	X					
Separation Force	X					
Unscrewing Torque		(b) (4) Nm (Twist)	ISO 11040-4:2015 Appendix G5	Results were reported to be 0.07 – 0.15 Nm. The sample size for the testing was 60.	X	
Ease of Assembly	X					
Resistance to Overriding		Force required to override (b) (4)	ISO 23908:2011, method acceptable	Complies; Sample size: 60	X	

Stress Cracking	X				
Validation of Graduation Markings	X				
Dead Space	X				
Coring Needle Test	X				
Anti-Needle Stick Performance testing ²		Needle safety system activation force: NLT (b) (4) N	ISO 23908:2011	2.2 – 3.3 N; Sample size 60	X
Connectivity to other devices necessary for use ³	X				
Injection force necessary to depress the plunger and eject the drug contents	X				
Tip cap removal force		Protective cover removal force: (b) (4) N	ISO 11040-4:2015	8.3 – 11.0 N; Sample size: 30	X
Piston seal blowback ⁴	X				
Sterility	X				

¹to 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.

²of 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).

³e.g., needles, adapters, transfer systems, extension tubing, luer connectors, and sharps prevention features

⁴ability of syringe with tip cap to hold a certain pressure on the piston

6.3.2. Environmental Conditioning Testing

All Essential Functional Requirements Evaluated under normal and stressed conditioning				
		Adequate	Inadequate	N/A
Normal/Anticipated Conditions	In-Use atmosphere	X		
	Last-Dose Accuracy			X
	Life-Cycle Testing	X		

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Challenge/Stressed Conditions	Free-Fall		X
	Dry heat/cold storage		X
	Damp Heat		X
	Cyclical		X
	Vibration		X

Breakloose and Glide force testing

The specifications for breakloose and glide force show that upper force limits and test results for breakloose force are about 2 fold lower than for glide force. Typically, breakloose force is either similar to or greater than glide force as can be seen in the force vs. distance graph in Annex E of ISO 11040-4:2015 *Glass barrels for injectables and sterilized subassembled syringes ready for filling*. A review of the submitted test protocol does not raise any concerns regarding the testing and the provided figure for *Typical plunger operation force-displacement graph* by TEVA shows a similar force vs. distance graph as in ISO 11040-4:2015. The following graph was provided:

Figure 5: Typical plunger operation force-displacement graph



It is likely that TEVA reported the maximum glide force recorded during the testing instead of an average gliding force. Since the glide force specification of NMT (b) (4)N is still well within what other manufacturers of similar products report, the test results and specifications of breakloose and glide force do not raise any concerns with regards to the usability of the prefilled syringe. Hence, this testing is acceptable.

Testing of EPRs after simulated shipping and aging

Teva conducted testing of devices aged to 4-years after simulated shipping. The Sponsor stated that the shipping plan was conducted per the ASTM testing schedule and that (b) (4) TEVA conducted a visual inspection and tested dose accuracy, breakloose / glide force, tip cap removal torque, and container closure integrity after shipping and aging. The following summary table was provided with the results:

Table 13: Functionality testing post-shipping testing of samples (b) (4)

Functionality Testing	Specification	Teva’s Proposed Combination Product (b) (4)	Results
Visual Appearance	(b) (4)	(b) (4)	Samples meet acceptance criteria
Dose Accuracy (expelled volume)	(b) (4) mL	(b) (4)	Samples meet acceptance criteria
Break Loose Force	Not more than (b) (4)N	(b) (4)	Samples meet acceptance criteria
Dynamic Glide Force	Not more than (b) (4)N	(b) (4)	Samples meet acceptance criteria
Tip Cap Removal Torque	(b) (4) Nm	(b) (4)	Samples meet acceptance criteria
Container closure integrity	(b) (4)	(b) (4)	Samples meet acceptance criteria

The conducted performance testing after simulated shipping and aging shows that the devices still meet the product specifications. Hence, this testing is acceptable. However, from the information provided, it is unclear how the simulated shipping studies were conducted. TEVA stated that the plan details were done according to the ASTM schedule, but did not cite a particular standard nor describe the actual simulated shipping modes. This information should be provided to evaluate the appropriateness of the conducted testing. Hence, an information request will be issued to the Sponsor to provide the shipping protocols and a citation of the utilized ASTM standard.

6.3.3. Biocompatibility Review

Biocompatibility Review Instructions

Biocompatibility Evaluation	
Materials List	Plunger Polystyrene (b) (4) grey plunger (b) (4)
	Syringe Body Type 1 Glass
	Needle Stainless Steel
	Accessories
Additives/Colorants	
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 <i>Notes:</i> 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 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.
Testing Performed	☐ Cytotoxicity ☐ Sensitization ☐ Irritation or Intracutaneous Reactivity ☐ Subacute/Subchronic Toxicity ☐ Genotoxicity ☐ Hemocompatibility ☐ Carcinogenicity

☐ Acute System Toxicity ☐ Material-Mediated Pyrogenicity				
Did the Sponsor provide a written justification in lieu of biocompatibility testing		☒ Yes	☐ No	☐ N/A
IS the written justification acceptable?		☒ Yes	☐ No	☐ N/A
<u>Review of Written Justification</u>				
The Sponsor provided letters of authorization (LOAs) for BD SafetyGlide Needle (K951254) and DMF (b) (4) for (b) (4) (b) (4) syringe. In addition, the TEVA has provided a statement of compliance to ISO10993 for the (b) (4) stopper. Biocompatibility of the individual components is demonstrated in either DMF (b) (4) or K591254. Since the prefilled syringe represents the primary container closure, biocompatibility of the fluid path is under the purview of CDER. An assessment of the externally communicating parts of the combination product is not necessary.				
Reviewer Comments/Conclusions				
Did the Sponsor perform the appropriate testing?		☐ Yes	☐ No	☐ N/A
<u>Review of Biocompatibility Testing</u>				
Reviewer Comments/Conclusions				
Did the Sponsor complete a chemical characterization?		☐ Yes	☐ No	☐ N/A
<u>Review of Chemical Characterization</u>				
Reviewer Comments/Conclusions				

Biocompatibility Stock IR

Design Verification Recommendation	
The Sponsor Provided Complete Design Verification for the Device Constituent	☐
The Sponsor DID NOT Provide Complete Design Verification for the Device Constituent	☒
Design Verification Information Requests	Section 11.3 Mid-Cycle IRs - #2 Section 11.4 Interactive IRs - #
All Information Requests were Resolved over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

7. RISK ANALYSIS

7.1. 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		

7.2. Summary of Risk Analysis

TEVA conducted a risk analysis to evaluate the critical tasks and use errors by the intended users (uFMEA), device design failure modes for the PFS and its packaging (dFMEA), and potential process failure modes (pFMEA). TEVA calculated the risk of each critical task or failure mode by combining the severity of harm with the probability of the critical task failing or failure mode occurring. Severities and probabilities were characterized utilizing the following criteria:

Table 12: Severity Scorings

Ranking	Severity of Harm	Possible Consequences
5	Catastrophic	Results in death to patient or third party
4	Critical	Results in permanent impairment or life- threatening injury to patient or third party
3	Serious	Results in injury or impairment requiring professional medical intervention to patient or third party
2	Minor	Results in temporary injury or impairment not requiring professional medical intervention to patient or third party
1	Negligible	Inconvenience or temporary discomfort to patient or third party
0	No Harm	No effect

Table 13: Occurrence Scorings

Score	Criteria	Frequency of Occurrence (Per application)
5	Frequent	Greater than or equal to 1: 1,000 ($\geq 10^{-3}$)
4	Probable	Less than 1:1,000, greater than or equal to 1:10,000 ($< 10^{-3}$ to $\geq 10^{-4}$)
3	Occasional	Less than 1: 10,000, greater than or equal to 1:100,000 ($< 10^{-4}$ to $\geq 10^{-5}$)
2	Remote	Less than 1 : 100,000, greater than or equal to 1 : 1,000,000 ($< 10^{-5}$ to $\geq 10^{-6}$)
1	Improbable	Less than 1 : 1,000,000 ($< 10^{-6}$)

The following tables of the residual risks were provided by the Sponsor:

Table 5: uFMEA Residual Risk Breakdown – conservative approach

			Qualitative Severity Levels					
			No Harm	Negligible	Minor	Serious	Critical	Catastrophic
			0	1	2	3	4	5
High	Frequent Likely to happen, often	5	0	0	0	0	0	0
Medium	Occasional, Can happen but not frequent	3	0	0	3	4	0	0
Low	Remote, Unlikely to happen, rare, remote	2	12	3	17	17	12	0

Table 6: dFMEA Residual Risk Breakdown

Combination Product risk profile following implementation of risk control measures			Qualitative Severity Levels					
			No Harm	Negligible	Minor	Serious	Critical	Catastrophic
			0	1	2	3	4	5
Semi-quantitative occurrence levels	Frequent	5	0	0	0	0	0	0
	Probable	4	0	0	0	0	0	0
	Occasional	3	0	0	0	0	0	0
	Remote	2	0	1	5	9	15	0
	Improbable	1	0	4	52	38	29	7

Table 7: pFMEA Residual Risk breakdown

Combination Product risk profile following implementation of risk control measures			Qualitative Severity Levels					
			No Harm	Negligible	Minor	Serious	Critical	Catastrophic
			0	1	2	3	4	5
Semi-quantitative probability levels	Frequent	5	0	0	0	0	0	0
	Probable	4	0	0	0	0	0	0
	Occasional	3	0	0	0	0	0	0
	Remote	2	0	5	43	19	0	0
	Improbable	1	1	18	74	128	185	7

The Sponsor performed a benefit risk analysis and stated that the benefits of using the device outweigh the residual risks associated with the device. In addition, TEVA stated that risks were mitigated to the lowest level possible and further modification of the device or the packaging are not expected to reduce error rates or user errors.

TEVA has not included a list of potential harms and mitigation strategies for the dFMEA and pFMEA, but stated that this documentation is contained in the DHF and is available upon inspection. However, the design verification and validation activities conducted by the Sponsor are typically considered sufficient to mitigate potential risks associated with a prefilled syringe. Hence, the information provided in the risk analysis is acceptable.

Risk Analysis Stock IR

Risk Analysis Recommendation	
The Sponsor provided complete Risk Analysis for the Device Constituent	☒
The Sponsor DID NOT provide There are Complete Response Deficiencies, See Section 13 Risk Analysis for the Device Constituent	☐
Risk Analysis Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #
All Information Requests were Resolved over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

8. LABELING

Pre-Filled Syringe Labeling Checklist

Attribute		Present		
		Yes	No	N/A
Device Type	Type	X		
	Syringe Size(s)	X		
	Needle Gauge	X		
	Needle Length	X		
	Quantity	X		
Prescription Statement under 801.109(b)(1), except for insulin syringes		X		
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;				X
Any instructions for using specialized syringes such as the anti-needlestick devices and cartridge syringes;				X
Any specific drug or biologic use;		X		
Instructions on how to clean and sterilize any reusable components.				X

8.1. Device Labels

INDIVIDUAL BLISTER PACK

(b) (4)

(RandomRepeat Printing)

Reviewer Comment

The labeling includes the manufacturers address, the contents of the packaging, a prescription statement, a statement that the device is for single use, and the length and gauge of the needle. All relevant device information is included, hence the labeling is acceptable.

8.2. Instructional Labeling

For each syringe:

1. Remove glass syringe barrel from tray and check that it is not damaged.
2. Remove perforated patient record label from syringe.
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.
4. Peel open the safety needle (SafetyGlide™) outer packaging.
5. Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully twist it until the cap disconnects for removal (see Figure 1).
6. Pull the cap (A) off in a straight upward direction. DO NOT TOUCH THE STERILE SYRINGE TIP (Luer-Lok) (B) (see Figure 2).
7. Attach the safety needle to the syringe tip (Luer-Lok). Twist needle until firmly seated (see Figure 3). 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.
8. Pull shield straight off needle to avoid damaging needle point.
9. Remove needle sheath.
10. Expel excess gas from the syringe (a small gas bubble may remain).
11. Administer intramuscularly slowly (1 to 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 4.
12. After injection, immediately activate the lever arm to deploy the needle shielding by applying a single finger stroke to the activation assisted lever arm by pushing the lever arm completely forward. Listen for a click. Confirm that the needle shielding has completely covered the needle (see Figure 5). NOTE: Activate away from self and others.

13. Discard the empty single use syringe into an approved sharps collector in accordance with applicable regulations and institutional policy.

14. Repeat steps 1 through 13 for second syringe.

Reviewer Comment

The instructions are concise and easy to understand. Hence, the instructions are acceptable.

8.3. Warnings/Precautions/Contraindications

CONTRAINDICATIONS

Fulvestrant Injection is contraindicated in patients with a known hypersensitivity to the drug or to any of its components. Hypersensitivity reactions, including urticaria and angioedema, have been reported in association with Fulvestrant Injection [see *Adverse Reactions (6.2)*].

WARNINGS AND PRECAUTIONS

Risk of Bleeding

Because Fulvestrant Injection is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.

Increased Exposure in Patients with Hepatic Impairment

The safety and pharmacokinetics of Fulvestrant Injection were evaluated in a study in seven subjects with moderate hepatic impairment (Child-Pugh class B) and seven subjects with normal hepatic function. Exposure was increased in patients with moderate hepatic impairment, therefore, a dose of 250 mg is recommended [see *Dosage and Administration (2.2)*].

Fulvestrant Injection has not been studied in patients with severe hepatic impairment (Child-Pugh class C) [see *Use in Specific Populations (8.6)*].

Injection Site Reaction

Injection site related events including sciatica, neuralgia, neuropathic pain, and peripheral neuropathy have been reported with Fulvestrant Injection. Caution should be taken while administering Fulvestrant Injection at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve [see *Dosage and Administration (2.3)* and *Adverse Reactions (6.1)*].

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, Fulvestrant Injection can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of fulvestrant to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at daily doses that are significantly less than the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive

potential to use effective contraception during treatment with Fulvestrant Injection and for one year after the last dose [see Use in Specific Populations (8.1), (8.3) and Clinical Pharmacology (12.1)].

Reviewer Comment

The Contraindications and Warnings to not pertain to the use of the device.

Labeling Recommendation	
The Sponsor provided complete Labeling for the Device Constituent	☒
The Sponsor DID NOT provide complete Labeling for the Device Constituent	☐
Labeling Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #
All Information Requests were Resolved over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

9. 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	(b) (4) mL	USP <697>
Audible / Visual information on injection status	N/A	N/A
Break Loose/Glide Force	NMT (b) (4) N / NMT (b) (4) N	ISO 11040-4 Annex E

Reviewer Comment

TEVA has included container contents and breakloose/glide force testing into the release specifications of the drug product. Since the entire contents of the syringe are intended to be injected, a fill volume specification for dose accuracy/expelled volume is adequate. The Sponsor has demonstrated that the syringe can deliver the container contents (b) (4) per ISO 11608-1:2014. Hence, the manufacturing control strategy is acceptable.

Release Specification Stock IR

Release Specifications Recommendation

The Sponsor provided complete Release Specifications for the Device Constituent		☒
The Sponsor DID NOT provide complete Release Specifications for the Device Constituent		☐
Release Specifications Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were Resolved over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

10.INTERACTIVE REVIEW

10.1. Filing Information Requests

Are there filing review information requests? No Yes

Agency Information Request #1 (Sent on 03/18/19) - ADEQUATE

In your response to the CR letter, you provided summary device verification data for dose accuracy, break loose / glide force, tip cap opening torque, protective cover removal force, needle safety system activation force, and force to override the safety mode. Furthermore, you have provided the test methods for break loose and glide force in 3.2.P.2. However, we were unable to locate the test methods for the other tests mentioned above and a description of the sample size. According to the 2013 FDA guidance “Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products”, test methods and procedures should be provided for combination product injectors. Please provide the following:

- Test methods for the conducted device verification testing; and
- A description of the sample size for each test

Sponsor Response (received on 03/19/2019)

As requested, courtesy copies of the test methods used for Design Verification testing are included in Module 3.2.P.2 of this Amendment. We refer the reviewer to Table 1 below that lists the parameters and the methods used to generate the data. As the testing is not routine, the methods used will not be maintained in the application going forward¹.

Table 1 – Design Verification Test Methods and Sample Size

Design Verification Test Parameter	Test Method Reference	Sample Size	Sample Size Justification
Dose Accuracy	18-136962-WI-12	60	Sample size as per ISO 11608-1:2014
Break Loose Force	18-136962-WI-14	60	Risk-based approach: Maximum severity 4 based on repeated missed dose or drug properties change
Dynamic Glide Force	18-136962-WI-14	60	Risk-based approach: Maximum severity 4 based on change in repeated missed dose or drug properties change
Tip Cap Opening Torque	18-136962-WI-6	60	Risk-based approach: Maximum severity 4 based on contamination issue

Protective cover removal force	18-136962-WI-11	30	Risk-based approach: Maximum severity 3 based on missed dose – single event
Needle safety system activation force	18-136962-WI-17	60	Risk-based approach: Maximum severity 4 based on repeated missed dose
Force required to override safety mode	18-136962-WI-18	60	Risk-based approach: Maximum severity 4 based on potential needle stick injury

Also as requested, sample sizes have been included for each parameter in Table 1 above. Sample sizes were determined by applying methodology within the referenced standards. If no methodology was listed within the standard, a risk-based approach was used to determine the sample size (ensuring a minimum of 30 samples was tested for each parameter).

The Clinical Hazards Analysis² assigns a risk severity category and ranking for each potential clinical hazard. If sample size was not listed in the standard and the risk-based approach was applied, the risk severity category was used to determine the risk severity ranking and sample size applied as listed in Table 2 below. In the event that multiple risks were associated with the parameter being tested, the highest severity ranking was used to ensure that the worst-case is evaluated.

Table 2 – Risk-based Approach Sample Size Determination

Risk Severity Category	Risk Severity Ranking	Recommended Sample Size
Catastrophic	5	150
Critical	4	60
Serious, Minor, Negligible	3, 2, 1	30

To clarify the methods used during design verification testing, the data presented previously in the CR response dated February 19, 2019 has been updated to reflect the test methods referenced above and included in Module 3.2.P.2 of this Amendment. We refer the reviewer to the [Summary of Design Requirements and Specifications for the PFS \(Including Needle\)](#) and [Summary of Validation/Verification and Manufacturing Control Strategy](#).

Reviewer Comments

TEVA provided test reports of the conducted performance tests and a description and justification of the chosen sample size. The Sponsor's response to this IR is complete. The chosen sample sizes for each test are acceptable.

10.2. 74-Day letter Information Requests

Are there 74-Day Letter information requests? No Yes

This section is not applicable

10.3. Mid-Cycle Information Requests

Are there Mid-Cycle review information requests? No Yes

Agency Information Request #2 (Sent on 05/21/19) - ADEQUATE

In your response to the CR letter you stated that a simulated shipping study was conducted (b) (4). However, you have not provided information on how these simulated shipping studies were conducted. This information is necessary to evaluate your reported test results post-shipping in table 13 of your CR response. Please provide a description or test protocol detailing how the simulated shipping studies were conducted. If you utilized an FDA recognized consensus standard for your testing (i.e. ASTM D4169-16) you may simply provide the distribution cycles tested, how the samples were conditioned (b) (4) and state any relevant deviations from the standard.

Sponsor Response (received on 05/24/19)

Teva acknowledges the Agency's request and as requested, Teva is providing herein a description detailing how the simulated shipping studies were conducted.

The simulated shipping study was performed in accordance with the FDA consensus standard ASTM D4169-

(b) (4)

Reviewer Comments

Teva stated that the shipping studies were conducted per ASTM D4169-16 *Standard Practice for Performance Testing of Shipping Container and Systems*. (b) (4)

(b) (4)

(b) (4) Since Teva stated that this testing covers the conditions the product is exposed to in the distribution channels, this is acceptable.

10.4. Interactive Review

Are there other interactive review information requests? No Yes

No	Yes

11.COMPLETE RESPONSE DEFICIENCIES

There are no outstanding unresolved information requests, therefore CDRH does not have any deficiencies for a CR Letter.

12.RECOMMENDATION

12.1. Recommendation to CDER/OHOP

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

12.2. Recommended Post-market commitments/post-market requirements

CDRH has Post-Market commitments/requirements	☐
CDRH does not have Post-Market commitments/requirements	☒

13.Appendix

13.1. Review of Responses to Facilities Questions

A review of the approvability as it relates to the facilities of the final combination product manufacturer is conducted in a separate memo.

END OF REVIEW

ICCR QUALITY SYSTEM REVIEW MEMO

Date: June 6, 2019

To: Mitchell Chan, Program Management, OND/OHOP/DOPI, CDER, WO22, Mitchell.Chan@fda.hhs.gov

CC: Office of Combination Product, Combination@fda.hhs.gov
Regulatory Business Program Manager (RBPM)/Regulatory Program Manager (RPM): Mitchell Chan, OND/OHOP/DOPI, CDER, WO22, Mitchell.Chan@fda.hhs.gov

Through: CDR Nikhil Thakur, OPEQ/OHT3/DHT3C, CDRH, WO 66, Rm 2518, nikhil.thakur@fda.hhs.gov

From: David Wolloscheck, OPEQ/OHT3/DHT3C/THT3C1, CDRH, WO 66, Rm 2533, David.wolloscheck@fda.hhs.gov

Applicant/Licensure: Teva Pharmaceuticals USA, Inc.
Morris Corporate Center III, 400 Interpace Parkway,
Parsippany, NJ, 07056, USA
[FEI]

Submission (Type & Number): NDA 210063

Combination Product Name: Fulvestrant injection PFS 250 mg/5 mL intramuscular injectable

Combination Product Indications for Use: Treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

Device Constituent (Type): Prefilled Syringe

ICCR Sharepoint Tracking Number: ICCR2019-04529

ICCR CTS Tracking Number: ICC1900169

Pre-Approval Facility Inspection: No

Documentation Review (Status): Complete

CDRH/OC Recommendation: Approvable

CDRH received a consult from CDER requesting the identification of the device manufacturing sites for NDA 210063 which will require a device inspection.

PRODUCT DESCRIPTION

Figure 1: Illustration of pre-filled syringe



The device constituent part of the combination product is a prefilled syringe. The syringe is operated by pushing or pulling on the plunger to inject or withdraw fluids.

REGULATORY HISTORY

The following facility was identified as being involved in the manufacturing and/or development of the combination product, Fulvestrant injection PFS 250 mg/5 mL intramuscular injectable, in [NDA 210063](#).

Combination Product Applicant

Firm Name: Teva Pharmaceuticals USA, Inc.

Address: Morris Corporate Center III, 400 Interpace Parkway, Parsippany, NJ, 07056, USA

FEI: [FEI]

Responsibility – As the applicant, Teva has the primary responsibility to ensure that all manufacturing is in compliance with the relevant sections of 21 CFR 820 (.20, .30, .50, and .100).

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.

Finished Combination Product Manufacturer

Firm Name: Actavis Italy S.P.A.

Address: Via Pasteur 10, 20014, Nerviano (Milan), Italy

FEI:3001116953

Responsibility – This firm is involved in major activities of the manufacture of the final finished combination product. Per the Sponsor, Actavis is responsible for manufacturing, packaging, labeling, and testing of the finished drug product for release, batch release, sterility and stability.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted 3/4/2019 to 3/15/2019. The inspection covered **drug CGMP** and was classified VAI.

Inspection Recommendation:

An inspection is not required because the manufacturing site does not require an inspection at this time given the risk of the combination product.

DOCUMENTATION REVIEW

Device Constituent Part Type: Prefilled Syringe

Device Constituent Part Class Class II: E.g. Prefilled Syringe, Auto Injector, Inhaler, Vaginal Ring, IUD

Combination Product NDA 210063 Proposed Indication for Use: Treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

1. Was the last inspection of the finished combination product manufacturing site, Actavis Italy S.P.A., OAI for drug or device observations?	YES ☐	NO ☒	NA ☐
2. Is the device constituent a PMA or class III device?	YES ☐	NO ☒	UNK ☐
3. Is the final combination product meant for emergency use?	YES ☐	NO ☒	UNK ☐

4. Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	YES ☒	NO ☐	UNK ☐
5. Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	YES ☐	NO ☒	UNK ☐
6. Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	YES ☐	NO ☒	UNK ☐
7. Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	YES ☐	NO ☒	UNK ☐

cGMP Risk: Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.

High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.

Though the combination product is intended to treat patient's with metastatic breast cancer, the device is not used in an emergency (i.e., the drug therapy spans two months and is conducted by a healthcare professional in a clinical setting). Furthermore, prefilled syringes are class II devices and are generally considered a low risk device. Hence, the overall risk of the device constituent part is low. Per a draft agreement with CDER, low risk, non-emergency combination products do not require a CDRH review of the facility when the manufacturer elects a streamlined compliance approach based on drug CGMPs. However, since this submission received a CR letter in part because of unresolved information requests by a CDRH compliance officer, the facility will receive a Quality Systems desk review to ensure that the concerns were addressed by the firm.

The Quality System requirements applicable to a particular manufacturer may vary based upon the type of constituent parts being manufactured and the aspects of their manufacture that are being performed at that site. All manufacturers are responsible for ensuring compliance with all requirements applicable to the manufacturing activities at their facilities. Where multiple

facilities bear responsibility for various aspects of the manufacturing process, only the holder of the application or clearance for the product is responsible for compliance with all aspects of the Quality System requirements applicable to the entire manufacturing process and across all facilities.

Applicant: Teva Pharmaceuticals USA, Inc.
Morris Corporate Center III, 400 Interpace Parkway, Parsippany,
NJ, 07056, USA
FEI: [FEI]

Finished Combination Product Manufacturer: Actavis Italy S.P.A.
Via Pasteur 10, 20014, Nerviano (Milan), Italy
FEI: 3001116953

(b) (4)

RECOMMENDATION

The application for NDA 210063 Fulvestrant injection PFS 250 mg/5 mL intramuscular injectable is approvable from the perspective of the applicable Quality System Requirements. The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

A routine surveillance inspection is recommended for the following facility to cover the relevant parts of the Quality Systems for a device-drug combination product manufacturer using a streamlined drug CGMP based approach:

- a. Actavis Italy S.P.A.

OC Decision: Approvable (Recommend approval to CDER)

Reviewer: _____

Branch Chief or Lead CSO: _____

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XIAOHONG CHEN
08/05/2019 06:41:20 PM

Recommendation: Complete Response

**NDA 210063
Review #1**

Drug Name/Dosage Form	Fulvestrant Injection
Strength	250mg/5ml (50mg/ml)
Route of Administration	Intramuscular
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceuticals USA, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA 0001	12/28/2016	DS/DP/Process/Micro/Biopharm/Facility
Multiple Categories 0003	03/31/2017	Process/Micro/Facility
Quality Amendment 0005	05/23/2017	DP/Process/Facility
Quality Amendment 0008	07/06/2013	DP/Process/Micro/Facility
Quality Amendment 0009	10/12/2017	Facility
Quality Amendment 0010	10/23/2017	Not reviewed due to late submission

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	CDER/OPQ/ONDP/DNDAPI
Drug Product	Amit Mitra	CDER/OPQ/ONDP/DNDPI
Process	Feiyan Jin	CDER/OPQ/OPF/DP/III
Microbiology	Koushik Paul	CDER/OPQ/OPF/DMA/MABI
Facility	Frank Wackes	CDER/OPQ/OPF/DIA/IABII
Biopharmaceutics	Parnali Chatterjee	CDER/OPQ/ONDP/DB
ORA	Caryn McNab	ORA/OO/OMPTO/DMPTPO/MDTP
Regulatory Business Process Manager	Kristine Leahy	CDER/OPQ/OPRO/DRBPMI
Application Technical Lead (ATL)	Xiao Hong Chen	CDER/OPQ/ONDP/DNDPI

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	3/2/2017	DMF was reviewed by Xianru Sun.
	Type III		Adequate	9/27/2017	DMF is not reviewed since adequate information is in the NDA.	
	Type V		Adequate	8/2/2016	DMF was reviewed by E. Berr	
	Type III		Adequate	5/27/2017 8/2/2017	DMF was reviewed by Jessica Hankins and Koushik Paul	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA 021344	NDA 021344	Listed Drug, Faslodex

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH	Finished	Deficient	9/18/2017	Sarah Mollo
CDRH Office of Compliance	Finished	Deficient	10/19/2017	Latoya Oliver -Powell

Clinical				
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the outstanding deficiencies in drug product, process, and the CDRH’s recommendation for the device, the OPQ quality team recommends “Complete Response” for the NDA.

The following deficiencies from the Quality Review team should be included in the action letter:

Drug Product

1. *Provide long term leachability data including the safety evaluation report of the leachable from the syringe components to cover the shelf life period. Alternatively, you may include the data from accelerated leachable studies.*
2. *Adopt specification for tensile and elongation of the plunger rod covering the shelf life as a part of quality control.*

Process

3.  (b) (4)
4. *We acknowledge that you provided the extractables/leachables study protocol for the . Please provide the study reports with data.*
5.  (b) (4)
6. 

7.

(b) (4)

8.

Combination Product

(b) (4)



CDRH

14. *The NDA does not include any design requirements and/or specifications for your prefilled syringe. The essential performance requirements should be included within the NDA. This should include, but is not limited to: the expelled volume (accuracy), breakloose force, glide force, and tip cap removal force. You may reference a master file or 510(k) for the actual verification testing (test reports, protocols, etc.). However, the expelled volume (dose accuracy), breakloose force, and glide force of the pre-filled syringe should be performed on the combination product including the drug product and the safety needle (i.e. same gauge and length) that is provided with the pre-filled syringe. Provide the design requirements and/or specifications for your prefilled syringe.*

15. *The table below represents the information needed to complete an adequate review of the device constituents. Provide this information, preferably in tabular format, for each essential performance requirement as specified in your design requirement documentation or provide a justification for why the testing is not necessary. The device requirements should include but are not limited to: deliverable volume (dose accuracy), break loose, glide force, and tip cap removal force.*

Essential Performance Requirement	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/Transportation (Y/N)	Lot Release Testing (Y/N)
Dose Accuracy	Ex: No less than 10 mL	{Insert Document Number}	{Insert Document Number}	{Insert Yes if specification was	{Insert Yes if specification was validated after shipping	{Insert Yes if specification is a

			or title of complete clinical study}	verified after aging the device to the labeled date of expiry}	or simulated shipping}	part of the lot release testing of the final finished combination product}
Needle Connection Type	Ex: ISO 11608-2					
Break loose						
Glide force						
Cap Removal Force	Ex: ≤ 15 N					
....						

16. *The syringes are presented in a tray with polystyrene plunger rod and SafetyGlide needles. You state that the BD Safety Glide™ Needle, is a Class II, 510(k) Medical Device cleared by the Center Devices and Radiological Health, U.S. FDA CDRH, under 510(k)#: K951254 and that therefore, no letter of access is needed for a 510(k) cleared Medical Device.” However, the needle is being supplied with the syringe and is therefore part of the combination product. The following information regarding the needle was not included within the submission:*

a. Include the design requirements and specifications in the NDA (i.e. length, gauge, connection type, material).

b. You may reference a master file or 510(k) for the verification testing; however, for the Agency to review the information within the K951254, you need to submit a letter of authorization (LOA) to review the information within the 510(k) to support the NDA.

c. In addition to performance testing per standards addressing the needle requirements (e.g. ISO 7864, ISO 9626, ISO 23908), the 510(k) should include a clinical use study mimics actual clinical use by patient substitutes rather than actual patients and helps evaluate the sharps injury prevention feature. The clinical use study helps to isolate problems with the device, optimize the device design, identify deficiencies in labeling and evaluate the type of training needed for device user. If the 510(k) does not provide a simulated use study, 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>

- d. The 510(k) should include a biocompatibility evaluation of the final finished needle component of the pre-filled syringe per the Agency guidance, Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". The endpoints evaluated should be based on the type and duration of contact. As your device is intended to deliver fluids systemically, the Agency recommends that the following endpoints are addressed: cytotoxicity, sensitization, and irritation, acute systemic toxicity, hemolysis, and material-mediated pyrogenicity. If the 510(k) does not evaluate the appropriate endpoints, additional testing may be needed.*
- 17. The release specifications submitted under section 3.2.P.5.1 do not include the breakloose and glide force. These specifications should be included in the release testing for the combination product. Update your release specifications to include the breakloose and glide force.*
- 18. The stability testing does not include the testing of the essential performance requirements of the device constituent of the combination product. Provide stability data supporting the proposed shelf-life of the combination product including testing of the expelled volume (i.e. dose accuracy), breakloose, and glide force of the combination product.*
- 19. The Agency was unable to locate a risk assessment of the combination product. Provide the 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. This should include planned mitigations of these risks, verification of risk mitigations, as well as the acceptability of remaining risks.*
- 20. A description of materials including the material composition (trade name and common name), material supplier, and whether the material is drug and/or patient contacting was not provided. Provide this information and include any additives, processing agents, colorants, etc.*

Please note that the wording of the CDRH OC deficiencies provided above (Combination Product deficiencies are slightly different from those provided in CDRH OC’s review. This is per OND signatory authority’s request and it has been agreed upon by the OPQ

facility review team. The changes of the wording do not affect the content and meaning of the CDRH OC's deficiencies.

Also note that the applicant submitted a Quality amendment (0010) dated 23-Oct-2017, five days prior to the PDUFA goal date, which does not have sufficient time for the FDA to conduct a comprehensive and complete review of the amendment. Therefore, the amendment has not been reviewed.

II. Summary of Quality Assessments

A. Product Overview

This is a 505(b)(2) NDA 210063 for Fulvestrant manufactured as a solution for injection with strengths of 250 mg/5 mL (50 mg/mL). The Listed Drug (LD) is Faslodex® (Fulvestrant) injection (NDA 21344). The API and its concentration, the route of the administration (IM), dose and the indications are the same as those of the LD. The only difference between the LD and the proposed drug product is the excipients used in the formulation. There is a USP monograph for Fulvestrant API. FASLODEX is an estrogen receptor antagonist indicated for 1) the treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy; 2) for the treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy and HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy. No other clinical studies have been conducted except that a BE study to demonstrate the bioequivalence between the LD and the proposed formulation.

Proposed Indication(s) including Intended Patient Population	Fulvestrant Injection is an estrogen receptor antagonist indicated for the: • Treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. • Treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	Recommended dose: • 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.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

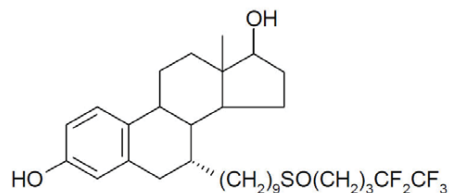
This is a 505(b)(2) NDA #210063 for Fulvestrant manufactured as a solution for injection with strengths of 250 mg/5 mL (50 mg/mL). Applicant refers to Type 2 DMF (b) (4) for quality information on Fulvestrant drug substance. The drug product is manufactured using (b) (4), and the product is provided in a pre-filled syringe. CDRH is consulted for the review of the syringe, and the review is in Panorama.

Drug Substance

International Non-proprietary Name (INN): Fulvestrant

Chemical Name: Estra-1,3,5(10)-triene-3,17-diol,7-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]-,(7 α ,17 β)
Or
7 α -[9-[(4,4,5,5,5-Pentafluoropentyl)sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17 β -diol

Structure:



Molecular Weight: 606.77

Fulvestrant is a synthetic organic substance, and has USP monograph. Fulvestrant USP is manufactured by (b) (4) and is supplied to be used in the manufacture of Fulvestrant for Injection or Infusion. The LD, FASLODEX[®] Injection, for this application was previously approved under NDA 021344. Following are the summary of DS information that is provided in this NDA.

The Applicant, Teva Pharmaceuticals, receives the DS from (b) (4) to manufacture drug product as solution formulation. Teva Pharmaceuticals refers to Type 2 DMF (b) (4) for quality information on Fulvestrant drug substance. The Type 2 DMF (b) (4) is currently Adequate. DMF (b) (4) was previously reviewed by Xianru Sun dated 03/02/2017, and was found to be Adequate for an ANDA. No other significant amendment is noted after 07/21/2017 for the DMF (b) (4). Therefore, no further review of the DMF (b) (4) is needed at this time for this NDA. From drug substance perspective, the quality information supports the NDA 210063 is found to be Acceptable.

Drug Product

Fulvestrant is not a new molecular entity. The fulvestrant injection is already approved under the tradename Faslodex Injection, 250 mg/5 ml. Teva chose the 505 (b)2 path since the inactive ingredients for the proposed drug product are different both qualitatively and quantitatively from that of the listed drug product (Faslodex Injection).

The recommended dose is 500 mg (two 5 ml injections of 250 mg/5 ml) administered intramuscularly one in each buttock (gluteal area), on days 1, 15, 29 and once monthly thereafter.

The proposed commercial primary packaging is a 5 ml clear, prefilled syringe with a grey rubber plunger similar to that of the listed drug. Applied overfill is equal to (b) (4)% in order to extract the labeled amount of solution.

Each pre-filled syringe contains 250 mg fulvestrant, USP. The inactive ingredients are dehydrated alcohol, USP (500 mg), benzyl alcohol, NF (500 mg), castor oil, USP (b) (4) mg), and medium chain triglyceride, NF (qs. to 5.0 ml). The LD is Faslodex (fulvestrant) Injection and it is also available in a 5 ml pre-filled syringe. Each 5 ml contains 250 mg fulvestrant, USP. The inactive ingredients for the LD in 5 ml are: Alcohol, (b) (4), benzyl alcohol, NF (b) (4), benzyl benzoate, USP (b) (4) mg), castor oil, USP (b) (4). The LD does not contain medium chain triglycerides. Therefore, the proposed drug product is different from that of the LD qualitatively and quantitatively. The qualification of medium chain triglycerides in the proposed level was consulted with the non-clinical reviewer for an intramuscular injection. The non-clinical reviewer is still reviewing the response from the applicant.

The registration batch sizes for two of the three batches is approximately (b) (4) kg (approximately (b) (4) theoretical 5 ml prefilled syringes). The third batch was manufactured at a pilot scale at approximately (b) (4) kg batch size (approximately (b) (4) theoretical units of prefilled syringes. The proposed commercial scale is approximately (b) (4) kg.

The proposed commercial primary container closure consists of a syringe (5 mL (b) (4) made of borosilicate colorless glass Type I Barrels with LUER Tip and Tip Cap). A safety glide needle, rubber plunger and plunger rod are also part of the container/closure system.

The drug product quality controls are conducted with the following quality attributes: Appearance, Clarity, Color, ID (HPLC by retention time, HPLC diastereoisomeric purity), Assay (HPLC), Uniformity of dosage units (USP<905>), Ethanol content (GC), Benzyl alcohol content (GC), Related compounds (HPLC), (b) (4) (NMT (b) (4) ppm), Visible particles (visual), Sub-visible particles (USP <788>), Bacterial endotoxin (USP<85>), Sterility (USP<71>), (b) (4)

The applicant has provided stability data for a maximum of 18 months under long term storage conditions ($5 \pm 3^{\circ}\text{C}$).

The storage condition is: Refrigerate, 2-8°C (36-46° F). Protect from light, store in the original carton until time of use. Based on 18 months long term stability data (5°C) and 6 months of accelerated stability data (25°C), the applicant is requesting a shelf life of 24 months. The proposed shelf life may be granted provided the applicant addresses the list of deficiencies included at the end of the review.

The information provided in the NDA is Not Acceptable due to the following two outstanding deficiencies to be included in the action letter. Also, the deliverable volume (dosing accuracy) specification should be applicable throughout the shelf life. Since CDRH has cited this item as a deficiency. No additional IR was sent and it would be captured in the CDRH review.

- 1) *Provide long term leachability data including the safety evaluation report of the leachable from the syringe components to cover the shelf life period. Alternatively, you may include the data from accelerated leachable studies;*
- 2) *Adopt specification for tensile and elongation of the plunger rod covering the shelf life as a part of quality control.*

Process

Fulvestrant Injection, 250 mg/5 mL (50 mg/mL) is a sterile intramuscular injection. (b) (4)

This NDA is Not Approvable per this process review. Several deficiencies were identified with regard to the DP manufacturing process development, in-process controls and tests, process validation, and they are provided below.

- 1) (b) (4)
- 2) *We acknowledge that you provided the extractables/leachables study protocol for the (b) (4). Please provide the study reports with data.*
- 3) (b) (4)
- 4) (b) (4)

5)

6)



(b) (4)

Microbiology

The microbiology review of the NDA consists of two DMF reviews, one in reference to the ANDA review conducted by the same microbiology reviewer and the relevant sections of the NDA review. The information that are not provided in the NDA but are referenced to support the NDA are described below:

➤



(b) (4)

➤



(b) (4)

- Microbiology review of the ANDA by Koushik Paul (A208730MR01.doc, dated 01/23/2017), regarding the container closure integrity test, facility and building, EM program, the initial validation studies for the autoclaves (AU.203 and AU.204), the initial validation studies for the A200 filling line, the actions concerning product when media fills fail and bacterial endotoxin method (*MA 9933AB*).

Review of microbiology related information in the NDA has concluded that microbial controls and sterility assurance of the  (b) (4) and controls of drug product release and stability are found to be Acceptable.

Facility

Drug Substance Facilities

Based on compliance history review and considering the proposed manufacturing to be conducted in at each site, the Drug Substance Manufacturing and testing facilities,



(b) (4)

(b) (4)

are deemed acceptable. Therefore, no Pre-approval inspection (PAI) is to be for the aforementioned three manufacturing sites.

Drug Product Facilities

Regarding the drug product manufacturing facility, ACTAVIS ITALY SPA (FEI#3001116953), the function performed for [REDACTED] (b) (4) is deemed acceptable. However, the function performed for the device controls (IDD / Manufacture of Injectable Delivery Device), is recommended "Withhold". See CDRH review and recommendation in Darrrts.

Combination Product:

- Per CDRH/OC Consult (ICC1700433 dated 19-October-2017) from Latoya Oliver-Powell, deficiencies were identified during the documentation review. Therefore, additional information from the firm is needed in order to complete the documentation review. Refer to the detailed list of deficiencies included at the end of this report.

Device Inspection:

- Actavis Italy S.p.A. Nerviano Plant (FEI 3001116953) was inspected for combination product manufacturing (IDD profile code). The firm did not have a device history file and so a Withhold was recommended. The CDRH/OC reviewer concurred with this initial recommendation. While the OMIR is Withhold in Panorama, this only reflects the device component of the application; the noted 820 deficiencies are all that need to be conveyed in the CR letter.
- Since the EIR for the October 2017 inspection of Actavis Italy S.p.A. Nerviano Plant (FEI 3001116953) is not available for review, it is recommended that during the next revision cycle, the IDD profile be re-evaluated in combination with the responses to the identified CDRH deficiencies.

Overall:

Consequently, while there are no drug manufacturing concerns, this facility is not acceptable for the intended commercial operations stated in NDA 210063 based upon deficiencies identified by CDRH during the course of the application review.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment

N/A

Application Technical Lead Name and Date:

Xiao Hong Chen, Ph.D.

25-Oct.-2017



Xiao
Chen

Digitally signed by Xiao Chen

Date: 10/25/2017 09:08:47PM

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MICROBIOLOGY

Product Background: Treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

NDA: 210063

Drug Product Name / Strength: Fulvestrant Injection, 50 mg/mL (250 mg/5 mL), supplied as single-use prefilled syringe.

Route of Administration: Intramuscular Injection

Applicant Name: Teva Pharmaceuticals USA, Inc.

Manufacturing Site: Actavis Italy S.p.A., Nerviano Plant, Via Pasteur 10, Milan, Nerviano, Italy-20014

Method of Sterilization: (b) (4)

Review Summary: The submission is **recommended** for approval on the basis of sterility assurance.

List Submissions being reviewed: 12/28/2016, 03/31/2017 and 07/06/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Supporting/Related Documents: > DMF # (b) (4) (Manufacturing Facilities in Nerviano, Italy; DMF is held by Actavis Italy S.p.A) was reviewed (15124mic3.doc, dated 03/14/2016) and later found adequate by E. Berr (15124mic3a1.doc, dated 08/02/2016).

> DMF # (b) (4) [titled (b) (4) (b) (4) Syringe Systems; DMF is held by BD medical-pharmaceutical system] regarding the sterilization and depyrogenation of the (b) (4) (b) (4) 5ml syringe barrels with (b) (4) rubber (b) (4) grey/plunger is reviewed by Jessica Hankins (D00501M45R01.doc , dated 05/27/2017) and Koushik Paul (D00501M48R01.doc, dated 08/02/2017) and found adequate.

> Microbiology review of the ANDA by Koushik Paul (A208730MR01.doc, dated 01/23/2017), regarding the container closure integrity test, facility and building, EM program, the initial validation studies for the autoclaves (AU.203 and AU.204), the initial validation studies for the A200 filling line, the actions concerning product when media fills fail and bacterial endotoxin method (*MA 9933AB*).

Concise Description Outstanding Issues Remaining: None.

Post-Approval Commitments:

Reviewer's Assessment: Not applicable

Lifecycle Management Considerations

Reviewer's Assessment: Not applicable

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date:

Koushik Paul, Ph.D. and 08/02/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Erika Pfeiler, Ph.D. and 08/02/2017



Koushik
Paul

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Date: 8/02/2017 03:08:09PM
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Erika
Pfeiler

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Date: 8/02/2017 03:10:36PM
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CHAPTER VII: BIOPHARMACEUTICS

NDA: 210063

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

Route of Administration: Intramuscular

Applicant Name: Actavis-Nerviano, Italy S.p.A

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

REVIEW SUMMARY:

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

➤ **OVERALL REVIEW RECOMMENDATION:**

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

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Parnali Chatterjee, PhD 10/2/2017

Secondary Reviewer Name and Date:

Okpo Eradiri, PhD 10/2/2017



Parnali
Chatterjee

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**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**

Date: September 18, 2017

To: Kristine Leahy, Regulatory Project Manager
Division of Oncology Products I (DOPI),
Office of Hematology and Oncology Products (OHOP),
Office of New Drugs (OND),
Center for Drug Evaluation and Research (CDER)

From: Sarah Mollo

Through: CDR Alan Stevens, Branch Chief
General Hospital Devices Branch

Subject: Consult for NDA 210063, ICC1700377

Applicant	Teva Pharmaceuticals
Indication for Use	Intramuscular Injectable for the treatment of breast cancer.
Drug / Biologic Constituent	Fulvestrant
Device Constituent	Pre-filled syringe (250mg/5ml)

Recommendation: Interactive review questions were sent to the sponsor on May 24, 2017 regarding the device constituent (see section V of this memo). The sponsor did not respond within the review clock. The following information is needed in order for CDRH to complete the review of the device constituent; therefore, I recommend that the following deficiencies be included in the CR letter:

1. The NDA does not include any design requirements and/or specifications. The essential performance requirements should be included within the NDA. This should include, but is not limited to: the expelled volume (accuracy), breakloose force, glide force, and tip cap removal force. You may reference a master file or 510(k) for the actual verification testing (test reports, protocols, etc). However, the expelled volume (dose accuracy), breakloose force, and glide force of the pre-filled syringe should be performed on the combination product including the drug product and the safety needle (i.e. same gauge and length) that is provided with the pre-filled syringe.
2. The table below represents the information needed to complete an adequate review of the device constituents. Please provide this information, preferably in tabular format, for each essential performance requirement as specified in your design requirement documentation or provide a justification for why the testing is not necessary. The device requirements should include but are not limited to: deliverable volume (dose accuracy), break loose, glide force, and tip cap removal force.

Essential Performance Requirement	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)

Dose Accuracy	Ex: No less than 10 mL	{Insert Document Number}	{Insert Document Number or title of completed clinical study}	{Insert Yes if specification was verified after aging the device to the labeled date of expiry}	{Insert Yes if specification was validated after shipping or simulated shipping}	{Insert Yes if specification is a part of the lot release testing of the final finished combination product}
Needle Connection Type	Ex: ISO 11608-2					
Break loose						
Glide force						
Cap Removal Force	Ex: ≤ 15 N					
....						

3. The syringes are presented in a tray with polystyrene plunger rod and SafetyGlide needles. You state that the BD Safety Glide™ Needle, is a Class II, 510(k) Medical Device cleared by the Center Devices and Radiological Health, U.S. FDA CDRH, under 510(k)#: K951254. Therefore, no letter of access is needed for a 510(k) cleared Medical Device.” However, the needle is being supplied with the syringe and is therefore part of the combination product.
- As the sponsor of the combination product submission, the design requirements and specifications should be included within the NDA (i.e. length, gauge, connection type, material).
 - You may reference a master file or 510(k) for the verification testing; however, for the Agency to review the information within the K951254, you need to submit a letter of authorization (LOA) to review the information within the 510(k) to support the NDA.
 - In addition to performance testing per standards addressing the needle requirements (e.g. ISO 7864, ISO 9626, ISO 23908), the 510(k) should include a clinical use study mimics actual clinical use by patient substitutes rather than actual patients and helps evaluate the sharps injury prevention feature. The clinical use study helps to isolate problems with the device, optimize the device design, identify deficiencies in labeling and evaluate the type of training needed for device user. If the 510(k) does not provide a simulated use study, please 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>
 - The 510(k) should include a biocompatibility evaluation of the final finished needle component of the pre-filled syringe per the Agency guidance, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"*. The endpoints evaluated should be based on the type and duration of contact. As your device is intended to deliver fluids systemically, the Agency recommends that the following endpoints are addressed: cytotoxicity, sensitization, and irritation, acute systemic toxicity, hemolysis, and material-mediated pyrogenicity. If the 510(k) does not evaluate the appropriate endpoints, additional testing may be needed.

4. 3.2.P.5.1 release specifications do not include the breakloose and glide force. The Agency recommends that these specifications are included in release testing. Please update your release specifications to include the breakloose and glide force.
5. The stability testing does not include the testing of the essential performance requirements of the device constituent of the combination product. Please provide stability data supporting the proposed shelf-life of the combination product including testing of the expelled volume (i.e. dose accuracy), breakloose, and glide force of the combination product.
6. The reviewer is unable to locate a risk assessment of the combination product. Please provide the location of or please provide the 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. This should include planned mitigations of these risks, verification of risk mitigations, as well as the acceptability of remaining risks.
7. Please provide a description of materials including the material composition (trade name and common name), material supplier, and whether the material is drug and/or patient contacting. Please include any additives, processing agents, colorants, etc.

Digital Signature Concurrence Table	
Reviewer	
Branch Chief	

I. Purpose / Background

The following consult request was included in sharepoint:

Consult for the syringe that was used as a container/closure for the drug product (pre-filled syringe).

II. Administrative

Documents Reviewed:

Cross-Referenced 510(k) #	Letter of Authorization Included in NDA / BLA	
	YES	NO
K951254		x

Document Title	Document Number	Date –Version	Location
User Requirement Specification	LA-EP2006_PFS_in X100L_URS_2	01/01/2016 – Version C	GSR Sequence 0000 / Section 3.2.P.7.2
Container Closure System			GSR Sequence 0000 / Section 3.2.P.7.
3.2.P.5.1 SPECIFICATIONS			GSR Sequence 0000 / Section 3.2.P.5

CDRH Review Team:

Team Member	Role	Deficiencies
Sarah Mollo (CDRH/ODE/GHDB)	Lead Reviewer – Biocompatibility Reviewer	#1-7

III. Device Description and Performance Requirements

Indications for Use	Fulvestrant Injection is an estrogen receptor antagonist indicated for the: • Treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. • Treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.

Route of 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. (2.2, 5.2, 8.6)

Device Characteristic	Description / Specification															
Syringe Barrel Material Type	<table border="1" style="width: 100%;"> <thead> <tr> <th style="width: 30%;"></th> <th style="width: 35%; text-align: center;">Component</th> <th style="width: 35%; text-align: center;">Manufacturer/Supplier</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">Syringes</td> <td>5 mL (b) (4) Syringe made of borosilicate colourless glass Type I Barrels with LUER Tip and Tip Cap</td> <td style="text-align: center;">(b) (4)</td> </tr> <tr> <td style="text-align: center;">Safety Glide Needle</td> <td>SafetyGlide™ NEEDLE SFTYGLD 21X1-1/2 RB TW</td> <td>Becton, Dickinson and Company BD Medical Surgical Systems</td> </tr> <tr> <td style="text-align: center;">Rubber Plunger</td> <td colspan="2" style="text-align: center;">(b) (4)</td> </tr> <tr> <td style="text-align: center;">Polystyrene Plunger rod</td> <td colspan="2" style="text-align: center;">(b) (4)</td> </tr> </tbody> </table>		Component	Manufacturer/Supplier	Syringes	5 mL (b) (4) Syringe made of borosilicate colourless glass Type I Barrels with LUER Tip and Tip Cap	(b) (4)	Safety Glide Needle	SafetyGlide™ NEEDLE SFTYGLD 21X1-1/2 RB TW	Becton, Dickinson and Company BD Medical Surgical Systems	Rubber Plunger	(b) (4)		Polystyrene Plunger rod	(b) (4)	
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Needle Specifications - Length(s) - Gauge(s) - Connection type - ISO 594 - Prestaked	Sent IR asking that the requirements and specifications (length, gauge, connection type) for the needle are included in the NDA and a LOA should be provided to review 510(k) for performance testing and biocompatibility testing. Give the needle standards as examples for testing.															
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Unclear if self-administration or health-care provider administration- clarify with CDER															
Residual Medication Volume	n/a															
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	Fulvestrant Injection, for intramuscular administration, is supplied as 250 mg/5 mL fulvestrant Dose is the entire syringe contents - one or two 5 mL injections (250 mg or 500 mg) depending on indication															
Storage conditions and expiry	REFRIGERATE, 2°-8°C (36°-46°F). TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE. No expiration date on labeling or in submission-sent IR for stability studies based on expiration date.															
Preparation and administration (describe all that are applicable) Warm to room temp	Instructions for Use in draft package insert: 2.3 Administration Technique Administer the injection according to the local guidelines for performing large															

prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc.	volume intramuscular injections. NOTE: Due to the proximity of the underlying sciatic nerve, caution should be taken if administering Fulvestrant Injection at the dorsogluteal injection site [see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]. The proper method of administration of Fulvestrant Injection for intramuscular use is described in the following instructions. <u>Preparation:</u> 1. Remove glass syringe barrel from tray and check that it is not damaged. 2. Remove perforated patient record label from syringe. 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. 4. Peel open the safety needle (SafetyGlide™) outer packaging. 5. Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully twist it until the cap disconnects for removal. 6. Pull the cap (A) off in a straight upward direction. DO NOT TOUCH THE STERILE SYRINGE TIP (Luer-Lok) (B) 7. Attach the safety needle to the syringe tip (Luer-Lok). Twist needle until firmly seated. 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. <u>For Administration:</u> 8. Pull shield straight off needle to avoid damaging needle point. 9. Remove needle sheath. 10. Expel excess gas from the syringe (a small gas bubble may remain). 11. Administer intramuscularly slowly (1-2 minutes/injection) into the buttock (gluteal area). <u>After Injection:</u> 12. After injection, immediately activate the lever arm to deploy the needle shielding by applying a single finger stroke to the activation assisted lever arm by pushing the lever arm completely forward. Listen for a click. Confirm that the needle shielding has completely covered the needle. NOTE: Activate away from self and others. 13. Discard the empty single use syringe into an approved sharps collector in accordance with applicable regulations and institutional policy. 14. Repeat steps 1 through 13 for second syringe.
Safety Features • Needle safety	“SAFETYGLIDE™ INSTRUCTIONS FROM BECTON DICKINSON SafetyGlide™ is a trademark of Becton Dickinson and Company.”

Reviewer Comment

The sponsor states that, “the BD Safety Glide™ Needle, is a Class II, 510(k) Medical Device cleared by the Center Devices and Radiological Health, U.S. FDA CDRH, under 510(k)#: K951254. Therefore, no letter of access is needed for a 510(k) cleared Medical Device.” The necessary information is not in the 510(k) summary; therefore, I sent an IR asking for the LOA and informed the sponsor they are responsible for ensuring the safety glide needle conforms to the recommendations in the guidance.

IV. Design Control Review

A. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer		X	
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X	
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer		X	
Validation Data		X	
Traceability Documentation		X	

*Sponsor may derive the regulatory requirements from 21 CFR 820.30 into multiple sets of documents. For example, injectors containing software may include separate software requirements and specification documents. In these circumstances, additional rows may need to be added to the table.

Reviewer Comment

The submission does not include any design requirements. The sponsor can reference 510(k)s, MAF, DMF, etc for data but the essential performance requirements should be included within the NDA. Send an IR asking for the device requirements and traceability matrix.

Traceability

The table below represents the information needed to complete an adequate review of the device constituents. Please provide this information, preferably in tabular format, for each essential performance requirement as specified in your design requirement documentation or provide a justification for why the testing is not necessary. The device requirements should include but are not limited to: deliverable volume (dose accuracy), break loose and glide force.

Essential Performance Requirement	Specification	Verification	Validation	Aging (Y/N)	Lot Release Testing (Y/N)
{Insert requirement} Ex: dose accuracy	{Insert specification }	{Insert Document Number}	{Insert Document Number}	{Insert Yes if specification was verified after aging the device to the labeled date of expiry}	{Insert Yes if specification is a part of the lot release testing of the final finished combination product}

Additionally, dose accuracy, breakloose, and glide force should be performed on the final finished combination product (i.e. with the drug product).

B. Design Verification and Validation Review

Standard / Guidance	Conforms			
	Yes	No	N/A	
Syringes	ISO 11040-4 Prefilled Syringes – Glass Barrel for Injectables			
	ISO 11040-5: Prefilled syringes - part			

	5: plunger stoppers for injectables.			
	ISO 7886, Sterile Hypodermic Syringes for Single Use;			
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use;			
	ISO 9626, Stainless Steel Needle Tubing for Manufacture of Medical Devices;			
Sharps Injury Prevention Feature	Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features			
	ISO 23908 - Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling			
Connections	ISO 594-1: Conical Fittings with 6% (Lure) Taper for Syringes, Needles and Certain Other Medical Equipment - Part 1: General Specifications			
	ISO 594-2: Conical Fittings with 6% (Lure) Taper for Syringes, Needles and Certain Other Medical Equipment - Part 1: Lock Fittings			

Reviewer Comment

1. An IR was sent requesting the pertinent information for the needle.

Design Verification Review

Essential Performance Requirement	Specification	Verification Test Results	
		PASS	FAIL
Break Force			
Glide Force			
Expelled Volume			
Tip Cap Removal			
Sharps Injury Protection – Simulated Use Testing			
Biocompatibility of Sharps Injury Prevention Feature per ISO 10993	Cytotoxicity		
	Irritation		
	Sensitization		
Stability and Simulated shipping/transportation Data adequately verifies device will meet essential			

performance requirements at expiry			

Reviewer Comment

1. IR sent requesting the verification testing on the final finished combination product.
2. I was unable to locate any stability testing for the essential performance requirements of the syringe (i.e. fill volume, breakloose, glide force). An IR was sent to request this information.
3. The sponsor states that, “the BD Safety Glide™ Needle, is a Class II, 510(k) Medical Device cleared by the Center Devices and Radiological Health, U.S. FDA CDRH, under 510(k)#: K951254. Therefore, no letter of access is needed for a 510(k) cleared Medical Device.” The necessary information is not in the 510(k) summary; therefore, I sent an IR asking for the LOA and tell the sponsor they are responsible for ensuring the safety glide needle conforms with the recommendations in the guidance. I will include references to the sharps guidance.

Design Validation Review

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product		x	

Reviewer Comment

The sponsor has not submitted a risk assessment for the combination product. An IR was sent requesting a risk analysis.

C. Labeling

Syringe Barrel Label	
Primary Package Label	

D. Design Transfer Activities – Release Specifications

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

Attribute	Specification	Test Method
Break Force	Not provided	
Glide Force	Not provided	
Dose Accuracy	NLT (b)(4)mL	USP <1>

Reviewer Comment

3.2.P.5.1 release specs do not include break loose and glide force, which are recommended release specifications for pre-filled syringes. Additionally, the directions are inject slowly over 1-2 minutes and the ability of the patient to follow these directions can be impacted by the b/l and g/f.

V. Information Requests – Sent 04/24/2017

2. The NDA does not include any design requirements and/or specifications. The essential performance requirements should be included within the NDA. This should include, but is not limited to: the expelled volume (accuracy), breakloose force, glide force, and tip cap removal force. You may reference a master file or 510(k) for the actual verification testing (test reports, protocols, etc). However, the expelled volume (dose accuracy), breakloose force, and glide force of the pre-filled syringe should be performed on the combination product including the drug product and the safety needle (i.e. same gauge and length) that is provided with the pre-filled syringe.
3. The table below represents the information needed to complete an adequate review of the device constituents. Please provide this information, preferably in tabular format, for each essential performance requirement as specified in your design requirement documentation or provide a justification for why the testing is not necessary. The device requirements should include but are not limited to: deliverable volume (dose accuracy), break loose, glide force, and tip cap removal force.

Essential Performance Requirement	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Dose Accuracy	Ex: No less than 10 mL	{Insert Document Number}	{Insert Document Number or title of completed clinical study}	{Insert Yes if specification was verified after aging the device to the labeled date of expiry}	{Insert Yes if specification was validated after shipping or simulated shipping}	{Insert Yes if specification is a part of the lot release testing of the final finished combination product}
Needle Connection Type	Ex: ISO 11608-2					
Break loose						
Glide force						
Cap Removal Force	Ex: ≤ 15 N					
....						

4. The syringes are presented in a tray with polystyrene plunger rod and SafetyGlide needles. You state that the BD Safety Glide™ Needle, is a Class II, 510(k) Medical Device cleared by the Center Devices and Radiological Health, U.S. FDA CDRH, under 510(k)#: K951254. Therefore, no letter of access is needed for a 510(k) cleared Medical Device.” However, the needle is being supplied with the syringe and is therefore part of the combination product.
 - e. As the sponsor of the combination product submission, the design requirements and specifications should be included within the NDA (i.e. length, gauge, connection type, material).
 - f. You may reference a master file or 510(k) for the verification testing; however, for the Agency to review the information within the K951254, you need to submit a letter of authorization (LOA) to review the information within the 510(k) to support the NDA.

- g. In addition to performance testing per standards addressing the needle requirements (e.g. ISO 7864, ISO 9626, ISO 23908), the 510(k) should include a clinical use study mimics actual clinical use by patient substitutes rather than actual patients and helps evaluate the sharps injury prevention feature. The clinical use study helps to isolate problems with the device, optimize the device design, identify deficiencies in labeling and evaluate the type of training needed for device user. If the 510(k) does not provide a simulated use study, please 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>
- h. The 510(k) should include a biocompatibility evaluation of the final finished needle component of the pre-filled syringe per the Agency guidance, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"*. The endpoints evaluated should be based on the type and duration of contact. As your device is intended to deliver fluids systemically, the Agency recommends that the following endpoints are addressed: cytotoxicity, sensitization, and irritation, acute systemic toxicity, hemolysis, and material-mediated pyrogenicity. If the 510(k) does not evaluate the appropriate endpoints, additional testing may be needed.
5. 3.2.P.5.1 release specifications do not include the breakloose and glide force. The Agency recommends that these specifications are included in release testing. Please update your release specifications to include the breakloose and glide force.
6. The stability testing does not include the testing of the essential performance requirements of the device constituent of the combination product. Please provide stability data supporting the proposed shelf-life of the combination product including testing of the expelled volume (i.e. dose accuracy), breakloose, and glide force of the combination product.
7. The reviewer is unable to locate a risk assessment of the combination product. Please provide the location of or please provide the 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. This should include planned mitigations of these risks, verification of risk mitigations, as well as the acceptability of remaining risks.
8. Please provide a description of materials including the material composition (trade name and common name), material supplier, and whether the material is drug and/or patient contacting. Please include any additives, processing agents, colorants, etc.

VI. Outstanding Deficiencies

See section V above, IRs sent March 24, 2017.

VII. Recommendation

The IRs sent on March 24, 2017 should be included in the CR letter.



Xiao
Chen

Digitally signed by Xiao Chen

Date: 10/25/2017 09:26:58PM

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