CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210063Orig1s000

OTHER REVIEW(S)

THRESHOLD ANALYSES REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	July 25, 2019
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 210063
Product Type:	Drug-Device Combination Product
Drug Constituent Name and Strength	Fulvestrant Injection, 250 mg/5 mL
Device Constituent:	Prefilled Syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Teva Pharmaceuticals USA, Inc. (Teva)
Submission Date:	February 19, 2019; May 31, 2019; and July 19, 2019
OSE RCM #:	2017-37-1
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS

1. REASON FOR REVIEW

This review evaluates the physical comparison, labeling comparison, and comparative task analysis submitted under NDA 210063 for Fulvestrant Injection to determine whether the sponsor needs to submit the results of a human factors validation study or a comparative human factor study as part of preapproval marketing submission. This is a combination product with a proposed prefilled syringe device constituent part that is intended to treat breast cancer. The listed drug is Faslodex (Fulvestrant) Injection, NDA 021344.

1.1. REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On December 28, 2016, Teva submitted a 505(b)(2) NDA 210063 for Fulvestrant Injection. Upon our evaluation of the submitted Fulvestrant Injection container label, carton labeling, and Prescribing Information (PI), we noted a difference in the tamper evident closure of the prefilled syringe cap between the proposed Fulvestrant Injection compared to the listed drug, Faslodex.[a] We noted that Teva did not submit a comprehensive use-related risk analysis, comparative analysis, or justification for why a human factors (HF) study is not needed to demonstrate the safe and effective use of the proposed Fulvestrant Injection. Subsequently, on October 26, 2017, NDA 210063 received a Complete Response (CR) letter that included recommendations for Teva to submit a comprehensive use-related risk analysis or comparative analysis and justification for why HF data is not needed to support the marketing application.

On February 19, 2019, Teva resubmitted NDA 210063 in response to the October 26, 2017 CR letter, and thus submitted a use-related risk analysis, a comparative analysis and justification for why HF data are not needed. On May 31, 2019, Teva submitted revised PI, container label, carton labeling and updated side-by-side container label and carton labeling comparisons to align with the recent changes made to the labels and labeling of the listed drug, Faslodex.

[a] Tingting, G. Label and Labeling Review for Fulvestrant NDA 210063. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 03. RCM No.: 2017-37.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Use-related risk analysis and Comparative analyses	C
Information Requests Issued During the Review	D
CDRH Human Factors Consult Review	E-N/A
Label and Labeling, Packaging	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide our evaluation of the comparative analyses, proposed PI, container label, and carton labeling for Fulvestrant Injection.

3.1. USE-RELATED RISK ANALYSIS

The sponsor submitted a use-related risk analysis (URRA) for Fulvestrant Injection prefilled syringe. We find that the tasks identified in the submitted URRA are comprehensive and appropriate for the use of the proposed product. We also agree with the Sponsor's categorization of critical tasks. We agree that the Sponsor assessed the risks associated with the critical tasks in the URRA and we agree with the Sponsor that the risks are mitigated by the overall product design, labels, and labeling. The sponsor submitted a comparative analysis to identify any differences which may affect the safe and effective use of the product as compared to the reference product in the intended users and use environment.

3.2. COMPARATIVE ANALYSES

Table 2 describes the sponsor's comparative analyses of their proposed product as compared to the reference product (RP) We reviewed the comparative task analysis and

physical comparison submitted on February 19, 2019. Additionally, we reviewed the revised labeling comparison analysis submitted on May 31, 2019.

Table 2. Comparative Analyses for Fulvestrant Injection and Faslodex				
	Differences Identified		Sponsor's Assessment of the Differences	DMEPA's Assessment of the Differences
	Proposed Product	Reference Product (RP)		
Physical Comparison - packaging	The product packaging is comprised of two separate trays[b], each holding one syringe and one SafetyGlide™ needle [redacted (b) (4)]	The product packaging is comprised of a single, white tray holding two syringes and two SafetyGlide™ needles	Providing the components in two separate, sterile trays may influence the dose the patient receives - both syringes must be used to deliver the full dose however, a user may interpret individual trays to mean only one syringe is needed per dose/patient. While the packaging format is different from the LD, the Teva product carton does contain both prefilled syringes, and the warning that 'both syringes must be administered to receive the full 500mg dose' is present on the carton, syringe label [redacted (b) (4)].	Teva proposes to package each syringe in a separate tray, whereas the RP packages two syringes in a single tray. We find that packaging each syringe in a separate tray may pose risk of underdose medication error because the single syringe per tray packaging may lead the HCP to believe there is only one syringe required to administer a full dose. However, the proposed configuration is found to be similar to other currently marketed products that are used by healthcare providers in the same use environment. Furthermore,

[b] Only one tray is pictured here, however there are two trays per carton.

			No new potential use errors or harms are introduced due to this design difference. The intended users of the product are Healthcare Professionals (HCPs), who are expected to be familiar with administering injectable medications and accustomed to navigating differences in user interfaces among drug products.	we find the inclusion of the statement, “both single-dose pre-filled syringes must be administered to receive the full 500 mg dose” on the proposed carton labeling and administration instructions clarify that both syringes are required to achieve a complete dose and this labeling mitigation has been found to be acceptable.
Physical comparison- cap	(b) (4)		These rib orientation differences facilitate the differing user interactions – to remove the cap of the LD the cap must be tilted backwards and forwards, whereas the TEVA product requires a twisting action.	The physical differences between the syringe caps lead to the differences in the user task, thus we combine our assessment of the physical and use task comparison for the cap. The

	(b) (4)			proposed Fulvestrant Injector prefilled syringe is fitted with a screw top cap that twists and turns to remove the cap from the prefilled syringe, whereas the RP prefilled syringe is fitted with a tamper evident tamper evident closure that is tilted back and forth until the cap is disconnected from the prefilled syringe.
Comparative Task Analysis-cap removal	Twist the cap counter-clockwise until the cap disconnects for removal.	Tilt cap back and forth (DO NOT TWIST CAP) until the cap disconnects for removal.	The design differences facilitate the differing user interactions – to remove the cap of the LD the cap must be tilted backwards and forwards, whereas the TEVA product requires a twisting action. HCPs who are used to handling different drug products that have different syringe caps. The risk posed to the user by the Teva product is considered to be comparable to the risk posed by the LD.	In this particular instance, we determined that these physical cap differences do not impact critical tasks. Additionally, based on similar products on the market, we expect that healthcare providers are likely to be familiar with disconnecting different type of screw top caps. Thus, we determined that these physical and task differences will not introduce any new risk and we agree with the sponsor's assessment and find these physical and task

				differences are acceptable.
Labeling Comparison –cap removal	Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully TWIST THE CAP COUNTER-CLOCKWISE until the cap disconnects for removal (see Figure 1). (b) (4)	Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully tilt cap back and forth (DO NOT TWIST CAP) until the cap disconnects for removal (see Figure 1).	Despite the instructions of the LD instruction to tilt/rock the cap and specifically stating 'DO NOT TWIST', the Teva product simply will not open (but is unlikely to be damaged) by the rocking action. Since the transparency of the Teva product cap allows for the screw threads to be seen, HCPs are likely to attempt to twist, even if the IFU is not read, particularly if initial attempts to tilt it off do not yield the expected result.	Our review noted that the differences in the labeling are required based on the physical differences in the cap designs and do not impact critical tasks. Thus, we find the proposed administration instructions acceptable from a medication error perspective.

3.3. Labels and Labeling

Our evaluation of the proposed Fulvestrant Injection PI did not identify any areas of vulnerability that may lead to medication errors. However, our review of the proposed Fulvestrant Injection container label and carton labeling identified the following areas of vulnerability that may contribute to medication errors:

- The format of the expiration date is not defined.
- There are two barcodes located in close proximity to each other on the container label.
- The human-readable and machine-readable (2D data matrix barcode) product identifiers are omitted from the smallest saleable unit

On July 17, 2019, we conveyed our container label and carton labeling recommendations for Fulvestrant Injection to Teva (see Appendix D). On July 19, 2019, Teva submitted revised Fulvestrant Injection container label and carton labeling in response to our recommendations. We find the revised Fulvestrant Injection container label and carton labeling submitted on July 19, 2019 acceptable from a medication error perspective.

3.4. COMMUNICATION OF DMEPA' S ANALYSIS TO OFFICE OF NEW DRUGS

DMEPA communicated our findings to the Division of Oncology Products 1 (DOP1) via e-mail on July 23, 2019. At that time, we also requested concerns that could inform our review. Per e-mail correspondence from DOP1 on July 24, 2019, they stated no additional concerns and did not object to DMEPA's recommendations.

4. CONCLUSION AND RECOMMENDATIONS

Based on our overall review of the URRA and comparative analyses between the proposed Fulvestrant Injection prefilled syringe and the RP, we agree with the sponsor that the use of the products is similar. The comparative analysis identifies a difference in packaging (e.g. 2 syringes per tray versus 1 syringe per tray in the proposed product) however, we find the labeling mitigations acceptable to communicate two syringes are required to administer one full dose. The comparative analyses identifies one use task difference (e.g. opening the syringe closure) which we do not find to be unique to the proposed product and find the intended user (e.g. HCP) to be familiar with a twist cap syringe closure. In addition, the URRA reflects that the known use risks have been addressed and the proposed product does not appear to introduce any new risks. As such, considering the totality of information provided, we agree that all potential risks involved in the use of Fulvestrant Injection have been considered and adequately mitigated to a reasonable level. Thus, we agree with sponsor's justification that results of a human factors validation study do not need to be

submitted as part of the marketing application. Lastly, we find the carton labeling and container label submitted on July 19, 2019 are acceptable from a medication error perspective.

4.1 RECOMMENDATIONS FOR TEVA

Based on our review of your use-related risk analysis (URRA), comparative analyses, and justification, we have determined that a human factors validation study is not needed to be submitted for Agency review. Please note that if you modify the product user interface prior to the approval of your marketing application, additional human factors considerations may apply.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Fulvestrant Injection received on May 31, 2019 from Teva, and the RP.

Table 3. Relevant Product Information for Proprietary name and the Listed Drug

Product Name	Fulvestrant Injection	Faslodex[c]
Initial Approval Date	N/A	April 25, 2002
Therapeutic Drug Class or New Drug Class	estrogen receptor antagonist	estrogen receptor antagonist
Active Ingredient	fulvestrant	fulvestrant
Indication	Monotherapy Fulvestrant Injection is indicated for the treatment of: •hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, or •HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. Combination Therapy Fulvestrant Injection is indicated for the treatment of: •HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal	Monotherapy Faslodex Injection is indicated for the treatment of: •hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, or •HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. Combination Therapy Faslodex Injection is indicated for the treatment of: •HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal

[c] Faslodex [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 JUN 12. Available from: https://www.accessdata fda.gov/drugsatfda_docs/label/2019/021344Orig1s039lbl.pdf.

	women in combination with ribociclib as initial endocrine based therapy or following disease progression on endocrine therapy. •HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.	women in combination with ribociclib as initial endocrine based therapy or following disease progression on endocrine therapy. •HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.
Route of Administration	Intramuscular	Intramuscular
Dosage Form	Injection	Injection
Strength	250 mg/ 5 mL (50 mg/mL)	250 mg/ 5 mL (50 mg/mL)
Dose and Frequency	500 mg to be administered intramuscularly into the buttocks (gluteal area) slowly (1 to 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter	500 mg to be administered intramuscularly into the buttocks (gluteal area) slowly (1 to 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter
How Supplied	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. The single-dose prefilled syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlide™) for connection to the barrel.	FASLODEX is supplied as two 5 mL clear neutral glass (Type 1) barrels, each containing 250 mg/5 mL of FASLODEX solution for intramuscular injection and fitted with a tamper evident closure. 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.	Refrigerate, 2°-8°C (36°-46°F). To protect from light, store in the original carton until time of use.

Container Closure/Device Constituent	a transparent, 5 mL glass syringe with luer connector, tip cap and rubber plunger stopper as a sterile, non-pyrogenic, preservative free, latex-free, solution for intramuscular use. The plunger stopper (b) (4)	(b) (4) Two of the labeled syringes assembled with plunger rods and (b) (4) together with two safety needles are packaged in plastic trays with lid which are then packed in printed folding cartons.
Intended Users	healthcare providers	healthcare providers
Intended Use Environment	Hospital or private healthcare facilities	Hospital or private healthcare facilities

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On June 12, 2019, we searched the L:drive and AIMS using the term, "fulvestrant" to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified 9 previous reviews[d,e,f,g,h,i,j,k,l], and we considered our previous recommendations to see if they are applicable for this current review.

[d] Tingting, G. Label and Labeling Review for Faslodex NDA 021344/S-039. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAY 15. RCM No.: 2019-386-1.

[e] Tingting, G. Label and Labeling Review for Faslodex NDA 021344/S-039. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 09. RCM No.: 2019-386.

[f] Tingting, G. Label and Labeling Review for Faslodex NDA 021344. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 07. RCM No.: 2018-2254.

[g] Tingting, G. Label and Labeling Review for Fulvestrant NDA 210326. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 04. RCM No.: 2018-1805-2.

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

[i] Tingting, G. Label and Labeling Review for Fulvestrant NDA 210326. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 07. RCM No.: 2018-1805.

[j] Tingting, G. Label and Labeling Review for Fulvestrant NDA 210063. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 03. RCM No.: 2017-37.

(b) (4)

[l] Tingting, G. Label and Labeling Review for Faslodex NDA 021344/S-033. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 09. RCM No.: 2016-2977.

APPENDIX C. COMPARATIVE ANALYSES

The comparative analyses submitted on February 19, 2019 can be accessed in EDR via:
\\cdsesub1\evsprod\nda210063\0014\m3\32-body-data\32r-reg-info\comb-prod-comp-analy-sdt-int1158.pdf

The use-related risk analysis submitted on February 19, 2019 can be assessed in EDR via:
\\cdsesub1\evsprod\nda210063\0014\m3\32-body-data\32r-reg-info\comb-prod-human-fact-summ-sdt-int1651.pdf

The revised container label and carton labeling comparisons submitted on May 31, 2019 can be accessed in EDR via:
\\cdsesub1\evsprod\nda210063\0021\m1\us\compare-carton.pdf
\\cdsesub1\evsprod\nda210063\0021\m1\us\compare-contain.pdf

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

DOP1 communicated our container label and carton labeling recommendations below to Teva on July 17, 2019.[m]

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

A. General Comments (Container Label & Carton Labeling)

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Container Label

1. As currently presented, there are two barcodes on the prefilled syringe container label. Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is

[m] Chan, M. NDA 210063 Fulvestrant C&C DMEPA Recommendations. Silver Spring (MD): FDA, CDER, OND, DOP1 (US); 2019 JUL 19.

confusing to the healthcare providers.[n] Therefore, we recommend you relocate the barcode that does not contain the NDC number away from the barcode containing the NDC number, and present it in a size that does not compete with, distract from the presentation of other required or recommended information on the label.

C. Carton Labeling

1. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[o] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

[n] Institute for Safe Medication Practices. Safety briefs: More barcodes than needed. ISMP Med Safe Alert Acute Care. 2014;19(2):1-3.

[o] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

APPENDIX F. PRODUCT SAMPLE, LABELS AND LABELING, AND PACKAGING

F.1 List of Labels and Labeling Reviewed and Images

Using the principles of human factors and Failure Mode and Effects Analysis,[p] along with postmarket medication error data, we reviewed the following Fulvestrant Injection labels and labeling submitted by Teva Pharmaceuticals USA, Inc. received on July 19, 2019.

- Container label
- Carton labeling
- Prescribing Information. Available from: \\cdsesub1\evsprod\nda210063\0025\m1\us\draft-pi.doc

Container Label

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

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

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

/s/

COLLEEN L LITTLE
07/29/2019 01:07:36 PM

LOLITA G WHITE
07/29/2019 01:19:23 PM

QUYNHNHU T NGUYEN
07/29/2019 01:21:29 PM

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

Date: October 19, 2017

To: Frank Wackes, Chemical Engineer,
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Through: Kendra Y. Jones, Lead Consumer Safety Officer,
DPLC/OC/CDRH
WO-66, Room 3631

Kendra Jones -A
2017.10.19 14:20:54 -04'00'

From: Latoya Oliver-Powell, Consumer Safety Officer,
CDRH/OC/D2/ASD

Applicant: Teva Pharmaceuticals USA, Inc.
Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054

Application # NDA 210063

Consult # ICC1700433

Product Name: Fulvestrant injection PFS 250mg/5ml Intramuscular Injectable

Pre-Approval Inspection: Yes

Documentation Review: Additional Information Required

Final Recommendation: **DELAY**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 210063.

REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

Inspection Recommendation

Actavis Italy S.p.A.
Via Luigi Pasteur 10
Nerviano Plant
Milan, Nerviano
Italy, 20014

FEI# 3001116953

Responsibility – Control release of drug product components (active drug substance, inactive ingredients, and container closure system), Manufacturing, packaging, labeling, and testing of the finished drug product for release, batch release, sterility and stability.

(b) (4)

Please Note: A review of OSAR revealed no previous inspections for the QSR. Based on this information, a pre- approval inspection of this site is recommended; however, CDRH OC will defer to CDER for the final decision.

DOCUMENTATION REVIEW

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

(b) (4)

MANUFACTURING

Production and Process Controls

The firm has not provided a summary of the procedures for environmental and contamination controls of the facility where manufacturing of the finished combination product occurs, or a description of how these conditions could adversely affect the finished combination product **(see deficiency #5 below).**

Production Flow

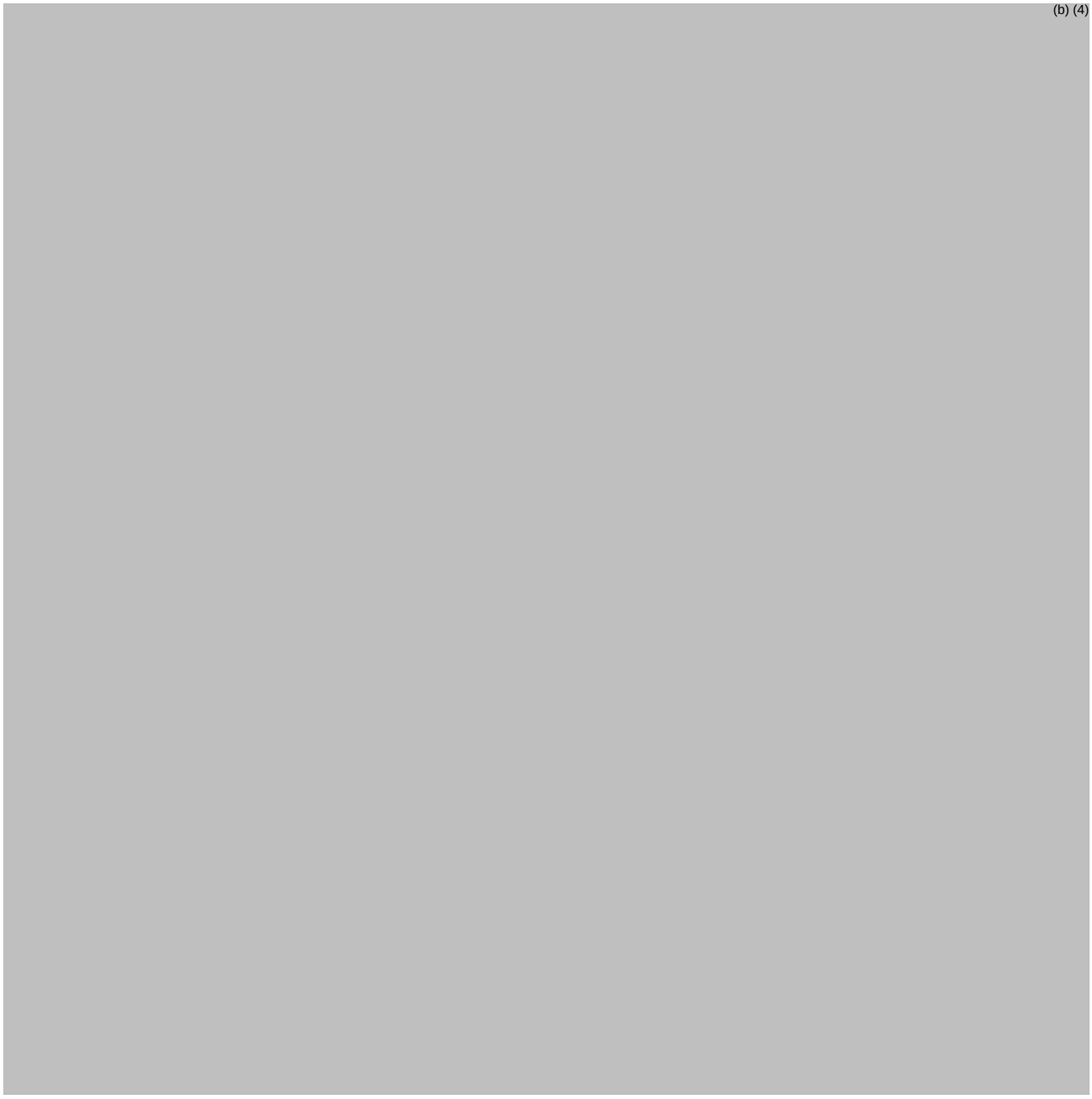
The information provided by the firm regarding production flow, appears to clearly identify the steps involved in the manufacture of the finished combination product.

Documentation Review Recommendation

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

Deficiencies to be conveyed to the applicant
The following deficiencies have been identified while doing the documentation review of the application, NDA 210063, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

(b) (4)



(b) (4)

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

RECOMMENDATION

Based on the information provided to the Office of Compliance for review, the application does not appear that the approvable from the perspective of the compliance of (b) (4). In addition, deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review. CDRH OC recommends a delay of approval and a pre-approval inspection of the Actavis Italy S.p.A to verify compliance as it relates to 21 CFR 820.

Latoya Oliver-powell -S

Digitally signed by Latoya Oliver-powell -S
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Date: 2017.10.19 14:24:05 -04'00'

Latoya Oliver-Powell

Prepared: LOliver-Powell: 10/18/17
Reviewed: KJones: 10/19/17

CTS No.: ICC1700433
NDA 210063

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

MEMORANDUM

To:	FDA Colleagues
From:	Tingting Gao, PharmD, DMEPA Safety Evaluator Chi-Ming (Alice) Tu, PharmD, DMEPA Team Leader QuynhNhu Nguyen, MS, DMEPA Associate Director Human Factors Danielle Harris, PharmD, BCPS, DMEPA Acting Deputy Director
Date:	October 3, 2017
Subject:	Fulvestrant Injection Label and Labeling Review Correction OSE RCM 2017-37 NDA 210063

After the initial Label and Labeling Review for NDA 210063 (RCM # 2017-37), dated June 2, 2017 was uploaded to DARRTS, an error was noted. Since the original Label and Labeling Review could not be deleted from DARRTS, an edited Label and Labeling Review with the same RCM number (2017-37) was uploaded in DARRTS on October 3, 2017.

For historical and tracking purposes, both versions of the memo are attached to this memorandum. However, the discussion contained in the June 2, 2017 review should be disregarded.

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	October 3, 2017
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 210063
Product Name and Strength:	Fulvestrant Injection, 250 mg/5 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Teva Pharmaceuticals USA, Inc.
Submission Date:	December 28, 2016
OSE RCM #:	2017-37
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS
DMEPA Associate Director Human Factors:	QuynhNhu Nguyen, MS
DMEPA Acting Deputy Director:	Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

Teva submitted a 505(b)(2) NDA 210063 for Fulvestrant Injection, and the listed drug is Faslodex (fulvestrant) Injection, NDA 021344.

Per the request of DOP1, we evaluates the submitted Fulvestrant Injection container labels, carton labeling, and Prescribing Information (PI) to identify areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We considered whether the proposed Fulvestrant product can be used safely and effectively as intended by the intended end users. Teva did not submit a comprehensive use-related risk analysis or justification for why a human factors (HF) study is not needed to demonstrate the proposed Fulvestrant can be used safely and effectively. However, we reviewed the materials and noted the only different feature in the use of the proposed 505(b)(2) Fulvestrant from Faslodex is the step to remove the prefilled syringe cap (See Table 2).

Table 2. Differences between the listed drug Faslodex and the proposed Fulvestrant Injection

	Faslodex (Listed Drug)	**Fulvestrant Injection (Proposed)**
How Supplied	Carton with two 5 mL clear neutral glass (Type 1) barrels, each containing 250 mg/5 mL of FASLODEX solution for intramuscular injection and **fitted with a tamper evident closure**.	Carton with 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**.

Table 2. Differences between the listed drug Faslodex and the proposed Fulvestrant Injection		
	Faslodex (Listed Drug)	**Fulvestrant Injection (Proposed)**
Instructions	**Step 5.** Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully tilt cap back and forth (DO NOT TWIST CAP) until the cap disconnects for removal (see Figure 1). (b) (4) 	**Step 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). Figure 1. (b) (4) 

The cap of the proposed Fulvestrant needs to be twisted for removal, whereas the Faslodex cap needs to be tilted back and forth for removal. Like Faslodex, end users of the proposed Fulvestrant are also healthcare providers. As such, we expect that healthcare providers are familiar with twist off caps given their experience with using various prefilled syringes that incorporate a twist off cap design. Thus, our evaluation found the proposed Fulvestrant's different cap and the steps for its removal to be common practice to the healthcare provider end users in the usual clinical setting, and we believe that the different cap and steps will not introduce any new risk.

On July 17, 2017, the Review Team decided NDA 021344 will receive a Complete Response (CR) for other issues. Given this NDA will head towards a CR, at the time of resubmission, Teva should submit a comprehensive use-related risk analysis and justification for not conducting a HF study.

3.1 PRESCRIBING INFORMATION

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

3.2 CONTAINER LABEL AND CARTON LABELING

We evaluated the proposed Fulvestrant Injection container label and carton labeling and determined that they are acceptable from a medication error perspective.

4 CONCLUSION

The proposed Fulvestrant Injection container label, carton labeling, and PI are acceptable from a medication error perspective.

However, as an additional comment in the non-approvability section of the CR letter, we request Teva to submit a comprehensive use-related risk analysis and justification for why HF data are not needed to demonstrate that the proposed Fulvestrant Injection can be used safely and effectively when they respond to the CR letter.

4.1 RECOMMENDATIONS FOR TEVA FOR INCLUSION IN THE NON-APPROVABILITY SECTION OF THE COMPLETE RESPONSE LETTER

We note that you have not submitted a comprehensive risk analysis or your justification for not conducting a Human Factors (HF) validation study.

We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures. If models of the same or similar combination products exist, your use-related risk analysis should incorporate applicable information on known use-related problems with those products. Useful information can be obtained from your own experience as well as from public sources such as literature, adverse event reports, and product safety communications (see draft guidance for industry Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development).

Additionally, if models of the same or similar combination products exist, it may be useful to conduct comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your proposed product and the comparator for the purposes of identifying what differences exist between the user interfaces and where the same or similar risks may apply to your proposed product.

Based on the aforementioned information and data, you should determine whether you need to perform a human factors (HF) validation study. If you determine that an HF validation study is not needed for your product, submit your risk analysis, comparative analyses, and justification for not conducting the HF validation study to the Agency for review under the NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Fulvestrant Injection that Teva Pharmaceuticals submitted on December 28, 2016, and the listed drug (LD) retrieved from July 12, 2016 approved Faslodex Prescribing Information[a].

Table 3. Relevant Product Information for Fulvestrant Injection and the Listed Drug Faslodex

Product Name	**Fulvestrant Injection**	**Faslodex** (NDA 021344)
Initial Approval Date	N/A	April 25, 2002
Active Ingredient	Fulvestrant	Fulvestrant
Indication	• 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	Intramuscular	Intramuscular
Dosage Form	Injection	Injection
Strength	250 mg/ 5 mL (50 mg/mL)	250 mg/ 5 mL (50 mg/mL)
Dose and Frequency	500 mg 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.	
How Supplied	Carton with 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**.	Carton with two 5 mL clear neutral glass (Type 1) barrels, each containing 250 mg/5 mL of FASLODEX solution for intramuscular injection and **fitted with a tamper evident closure**.
Storage	REFRIGERATE, 2°-8°C (36°-46°F). To protect from light, store in the original carton until time of use.	

[a] Faslodex. Drugs@FDA. U.S. Food and Drug Administration; July 2016. [cited 2017 MAR 27]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021344s029lbl.pdf.

Table 3. Relevant Product Information for Fulvestrant Injection and the Listed Drug Faslodex		
Product Name	**Fulvestrant Injection**	**Faslodex** (NDA 021344)
Container Closure	5 mL pre-filled syringe barrel with luer connector and tip cap	The FASLODEX PFS consists of a [redacted] (b) (4) with a tamper evident closure [redacted] (b) (4) a polystyrene plunger rod and a [redacted] (b) (4)

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On March 29, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

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

D.2 Results

Our search did not retrieve any results.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Fulvestrant Injection labels and labeling submitted by Teva on December 28, 2016.

- Container label
- Carton labeling
- Prescribing Information (image not shown)

G.2 Label and Labeling Images

Container Label

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

Carton Labeling

(b) (4)

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/s/

TINGTING N GAO
10/04/2017

CHI-MING TU
10/04/2017

DANIELLE M HARRIS on behalf of QUYNHNHU T NGUYEN
10/04/2017

DANIELLE M HARRIS
10/04/2017

M E M O R A N D U M

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

DATE: 8/16/2017

TO: Office of New Drugs
Division of Oncology Products (DOP1)

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

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

RE: NDA 210063

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

Rationale

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

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Watson Therapeutics, Inc.	3400 Enterprise Way, Miramar, FL

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/s/

ANGEL S JOHNSON
08/21/2017

M E M O R A N D U M

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

DATE: July 19, 2017

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

Julia Beaver, M.D.
Director (Acting)
Division of Oncology Products (DOP1)
Office of Hematology and Oncology Products
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

and

Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

SUBJECT: Amended EIR review for the surveillance inspection of (b) (4)

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of studies ACT-15160 (NDA 210063), (b) (4)

(b) (4)

No significant deficiencies were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

The evaluation of inspectional finding was provided in the review dated June 21, 2017. This review is being amended to correct the study number, study title, and dates of conduct for study ACT-15160 (NDA 210063) under the "Inspected Studies" section of this review.

The conclusion remains the same as provided in the initial review.

Inspected Studies:

NDA 210063

Study Number: ACT-15160
Study Title: "An open label, randomized, parallel group, single dose, bioequivalence study of fulvestrant injection 50 mg/mL in healthy, adult, human female subjects in fasting conditions."
Dates of conduct: (b) (4)

ANDA (b) (4)

Study Number: (b) (4)
Study Title:

Dates of conduct: (b) (4)

Study Number: (b) (4)
Study Title:

Dates of conduct: (b) (4)

Study Number:
Study Title: (b) (4)

Dates of conduct: (b) (4)

ANDA (b) (4)

Study Number:
Study Title: (b) (4)

Dates of conduct: (b) (4)

ANDA (b) (4)

Study Number:
Study Title: (b) (4)

Dates of conduct: (b) (4)

Study Number:
Study Title: (b) (4)

Dates of conduct: (b) (4)

ANDA (b) (4)

Study Number:
Study Title: (b) (4)

(b) (4)

Dates of conduct: (b) (4)

Study Number:
Study Title: (b) (4)

Dates of conduct: (b) (4)

ANDA (b) (4)

Study Number:

Study Title: (b) (4)

Dates of conduct: (b) (4)

Study Number:
Study Title: (b) (4)

Dates of conduct: (b) (4)

ANDA (b) (4)

Study Number:
Study Title: (b) (4)

Dates of conduct: (b) (4)

Study selected and audited as a part of OSIS surveillance program from the list of bioequivalence studies provided by (b) (4), during the inspection

Study not yet submitted to the Agency:

Study Number:
Study Title: (b) (4)

Dates of conduct: (b) (4)

Analytical site: (b) (4)

OSIS scientists Arindam Dasgupta, Ph.D., Deputy Director and Gajendiran Mahadevan, Ph.D., Pharmacologist audited the analytical portion of the above studies at (b) (4).

(b) (4)

At the conclusion of the inspection, we did not observe any objectionable findings and did not issue Form FDA 483 to the analytical site.

Conclusion:

After reviewing the inspectional findings, we conclude the data from the audited studies are reliable. Therefore, we recommend that the data from studies ACT-15160 (NDA 210063), (b) (4)

(b) (4)

Based on the inspectional findings, studies of similar design conducted between the last inspection [redacted] (b) (4) and the end of the current surveillance interval should be accepted for review by the Agency without an inspection.

Gajendiran Mahadevan, Ph.D.
Pharmacologist

Arindam Dasgupta, Ph.D.
Deputy Director, DNDBE

Final Classification:

NAI: [redacted] (b) (4)
FEI# [redacted] (b) (4)

cc:
OTS/OSIS/Kassim/Choe/Kadavil/CDER-OSIS-BEQ@fda.hhs.gov
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Mahadevan
OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au

Draft: GM 07/18/2017
Edits: CB 07/19/2017

ECMS:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f880fa451e

OSIS File #: BE 7444 (NDA 210063); [redacted] (b) (4) (b) (4)

FACTS: [redacted] (b) (4)

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/s/

GAJENDIRAN MAHADEVAN
07/19/2017

ARINDAM DASGUPTA
07/19/2017

CHARLES R BONAPACE
07/19/2017

M E M O R A N D U M

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

DATE: June 21, 2017

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

Julia Beaver, M.D.
Director (Acting)
Division of Oncology Products (DOP1)
Office of Hematology and Oncology Products
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

and

Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

SUBJECT: Surveillance inspection of (b) (4) (b) (4)

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of studies ACT-15160 (NDA 210063), (b) (4) (b) (4)

No significant deficiencies were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, we conclude the data from the audited studies ACT-15160, [redacted] are reliable. Thus, we recommend that the data from the audited studies and other studies of similar design be accepted for further Agency review.

Inspected Studies:

NDA 210063

Study Number: ACT-15106
Study Title: "An open label, randomized, parallel group, single dose, bioequivalence study of fulvestrant injection 50 mg/mL in healthy, adult, human subjects."
Dates of conduct: [redacted]

ANDA [redacted]

Study Number:
Study Title: [redacted]

Dates of conduct: [redacted]

Study Number:
Study Title: [redacted]

Dates of conduct: [redacted]

Study Number: (b) (4)
Study Title:

Dates of conduct: (b) (4)

ANDA (b) (4)

Study Number: (b) (4)
Study Title:

Dates of conduct: (b) (4)

ANDA (b) (4)

Study Number: (b) (4)
Study Title:

Dates of conduct: (b) (4)

Study Number: (b) (4)
Study Title:

Dates of conduct: (b) (4)

ANDA (b) (4)

Study Number: (b) (4)
Study Title:

[redacted]S

Dates of conduct: [redacted]

Study Number:
Study Title: [redacted]

Dates of conduct: [redacted]

ANDA [redacted]

Study Number:

Study Title: [redacted]

Dates of conduct: [redacted]

Study Number:
Study Title: [redacted]

Dates of conduct: [redacted]

ANDA [redacted]

Study Number:
Study Title: [redacted]

Dates of conduct: [redacted]

Study selected and audited as a part of OSIS surveillance of bioequivalence studies provided by [redacted], during the inspection

Study not yet submitted to the Agency:

Study Number: [redacted]
Study Title: [redacted]

Dates of conduct: [redacted]

Analytical site: [redacted]

OSIS scientists Arindam Dasgupta, Ph.D., Deputy Director and Gajendiran Mahadevan, Ph.D., Pharmacologist audited the analytical portion of the above studies at [redacted]

[redacted]

At the conclusion of the inspection, we did not observe any objectionable findings and did not issue Form FDA 483 to the analytical site.

Conclusion:

After reviewing the inspectional findings, we conclude the data from the audited studies are reliable. Therefore, we recommend that the data from studies ACT-15160 (NDA 210063), [redacted] be accepted for further review.

Based on the inspectional findings, studies of similar design conducted between the last inspection (b) (4) and the end of the current surveillance interval should be accepted for review by the Agency without an inspection.

Gajendiran Mahadevan, Ph.D.
Pharmacologist

Arindam Dasgupta, Ph.D.
Deputy Director, DNDBE

Final Classification:

NAI: (b) (4)

cc:
OTS/OSIS/Kassim/Choe/Kadavil/CDER-OSIS-BEQ@fda.hhs.gov
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Mahadevan
OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au

Draft: GM 06/19/2017; 06/21/2017
Edits: AD 06/19/2017; CB 06/20/2017

ECMS:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f880fa451e

OSIS File #: BE 7444 (NDA 210063); (b) (4)

FACTS: (b) (4)

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/s/

GAJENDIRAN MAHADEVAN
06/21/2017

ARINDAM DASGUPTA
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