CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210063Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210063

COMPLETE RESPONSE

Teva Pharmaceuticals USA, Inc.
Attention: Joann Stavole, MS, RAC
Senior Director, Regulatory Affairs
Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054

Dear Ms. Stavole:

Please refer to your New Drug Application (NDA) dated December 28, 2016, received December 28, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Fulvestrant Injection, 250 mg/5 mL.

We also acknowledge receipt of your amendment dated October 23, 2017, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

NONCLINICAL

1. The safety of the proposed level of the medium chain triglycerides (MCT) excipient in the drug product to be administered by intramuscular injection was not adequately justified. The potential impact of this excipient on local tissue toxicities as it compares to the listed drug was not adequately addressed. You may not rely on information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries to justify a safe level of an excipient. MCT were not listed as a component of the vehicle or in the Certificate of Analysis in the reports for the rat and rabbit toxicology studies conducted with fulvestrant intramuscular injection and submitted to your NDA. The levels and fatty acid composition of the MCT administered to rats and rabbits in your fulvestrant injection studies were not provided. Therefore, these studies were inadequate to assess the safety of intramuscular injection of the proposed levels of MCT present in your to-be-marketed Fulvestrant Injection drug product. Provide an adequate justification for the safety of the proposed levels of MCT in your drug product administered by intramuscular injection. We recommend that you submit a final report from a GLP nonclinical bridging toxicology study in a single species comparing your Fulvestrant Injection formulation to the listed drug product (Faslodex) at a clinically relevant

dose. This study should include assessment of local tissue effects (macro and microscopic) and toxicokinetics following repeated intramuscular injections.

PRODUCT QUALITY

Drug Product

2. 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.

3. Adopt specification for tensile and elongation of the plunger rod covering the shelf life as a part of quality control.

Process

4. (b) (4)

5. We acknowledge that you provided the extractables/leachables study protocol for the (b) (4). Provide the study reports with data.

6. (b) (4)

7. (b) (4)

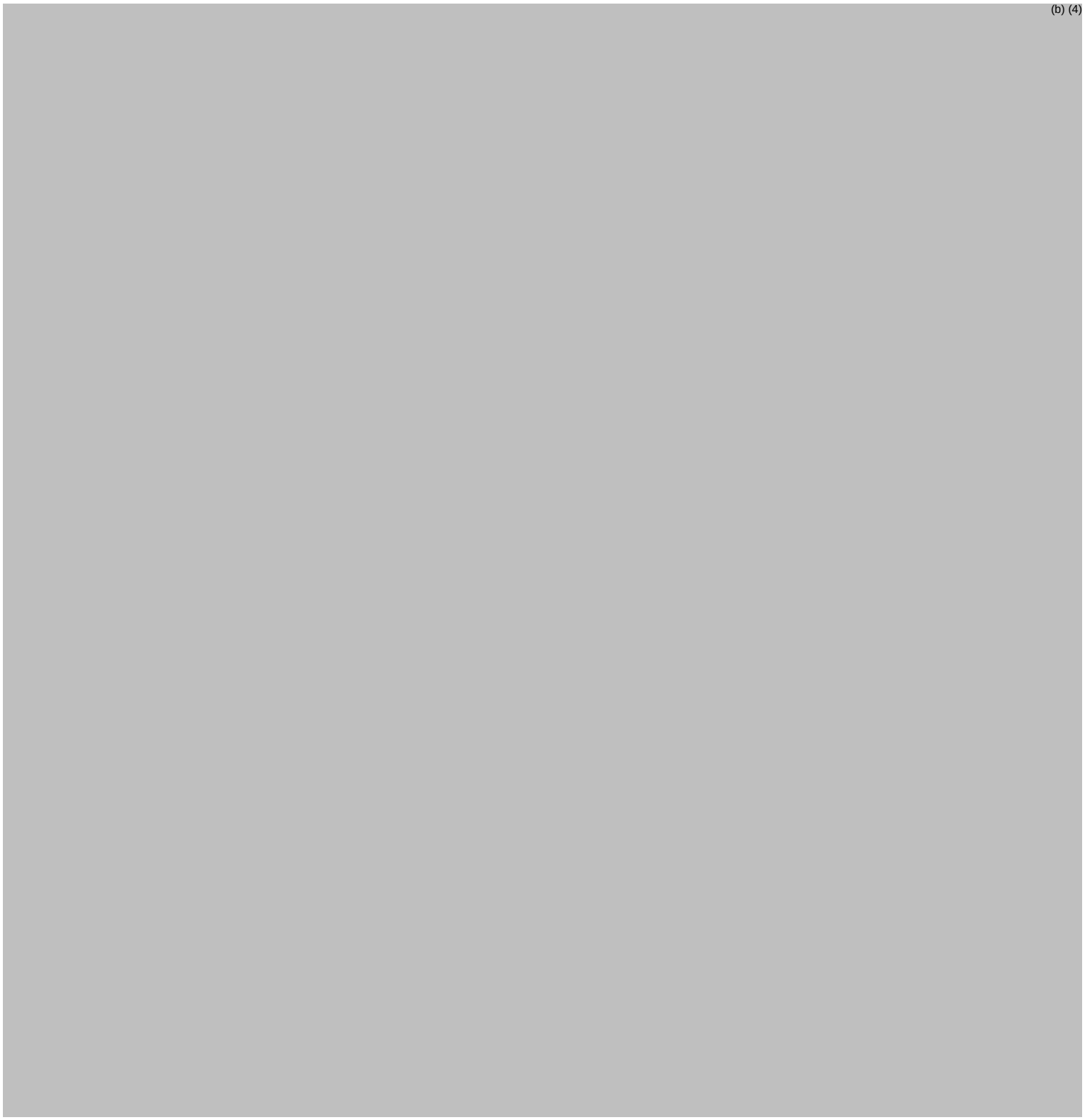
8. (b) (4)

9. (b) (4)

Combination Product

(b) (4)

(b) (4)



Device

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

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.

PRESCRIBING INFORMATION

22. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

    If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

23. Submit draft carton and container labeling with your resubmission.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. 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.

2. You may find useful information regarding the types of documents to provide in a Guidance document: '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

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Sakar Wahby, Regulatory Project Manager, at (240) 402-5364.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, MD
Deputy Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

AMNA IBRAHIM
10/26/2017