



Our STN: BL 125700/0

COMPLETE RESPONSE

APRIL 24, 2020

FKD Therapies, Oy
Attention: Elizabeth Wishart, B.Sc., MBA
Mapi USA, Inc.
2343 Alexandria Drive, Suite 100
Lexington, KY 40504

Dear Ms. Wishart:

Please refer to your Biologics License Application (BLA) submitted February 26, 2019 and received, September 3, 2019, for nadofaragene firadenovec manufactured at your Kuopio, Finland location and submitted under section 351(a) of the Public Health Service Act.

We have completed our review of all the submissions you have made relating to this BLA with the exception of the information in amendments BL 125700/0.41, 0.42, and 0.43 submitted March 13, 2020, March 31, 2020, and April 15, 2020, respectively. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

Chemistry, Manufacturing, and Controls (CMC):

1. CBER conducted a Pre-License Inspection (PLI) of the FinVector Oy facility from January 20-25 and January 27-28, 2020, and issued a Form FDA 483, List of Inspectional Observations. Your responses to the FDA 483 received through March 2, 2020, do not sufficiently address the concerns noted during the inspection as your corrective actions do not appear to be comprehensive enough to address the systemic issues. Examples include:
 - Investigations of deviations do not include a comprehensive evaluation to determine the impact on product safety, and initiation of corrective actions to prevent recurrence of issues is not consistently performed.
 - Your manufacturing procedures are not sufficiently detailed to provide consistent lot-to-lot reproducibility of your finished product.
 - The cleaning and disinfection are not fully validated to demonstrate that the cleaning agents are effective, and that fumigation decontamination is effective for viral inactivation.

- There is lack of assurance of the accuracy of certain test results, including sterility. Your storage and shipping conditions of the sterility samples are not controlled or validated to sufficiently demonstrate that the sample has not been altered prior to testing.

The observations described in the Form FDA 483 issued at the close of the inspection referenced above are an indication of your quality unit not fulfilling its responsibility to assure the identity, strength, quality, and purity of nadofaragene firadenovec. Approval of a biologics license application or issuance of a biologics license constitutes a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products. Applicable requirements for the maintenance of establishments for the manufacture of a product include, but are not limited to, the good manufacturing practice requirements. Your corrective actions need to be more comprehensive with respect to addressing the underlying quality oversight issues, and a second PLI will be necessary to verify the corrective actions once they have been fully implemented.

2. Aseptic process validation (b) (4), successful media fills) was not completed prior to manufacture of your Process Performance Qualification lots. Please repeat these runs after the media fill acceptance criteria have been updated and any operator re-training as required based on changes to the aseptic process procedures, in particular but not limited to, 483 Observations 5 and 10. Please submit the media fill report following completion of the media fill runs to support your commercial manufacturing process.
3. Sterility assurance of the product contact equipment and surfaces has not been demonstrated based upon the review of the sterilizing autoclave final report (b) (4) Validation Summary Report GMP (b) (4), GMP, Revalidation 2018 and associated data run sheets. The testing documentation in the report is inadequate to ensure that all surfaces have been adequately sterilized. Please provide documentation and data demonstrating exact placement of (b) (4) during testing. The information should include diagrams or photos of (b) (4) and (b) (4) placement, as well as detailed descriptions of how the (b) (4) items were prepared (i.e., size and type of bag used, double bag, quantity of items inside, any wrapping, tubing diameter and length, etc.). The detailed item (b) (4) description from validation testing should be added to the (b) (4) operating procedure to ensure items are prepared and (b) (4) in the same manner as validated.
4. Equipment operating parameters established after qualification are not detailed in the manufacturing procedures and/or batch records to ensure consistent operation of equipment within qualified parameters. In addition, equipment qualification deviations have not been resolved to ensure there is no impact on performance validation or process validation testing. The use of inconsistent

operating parameters across multiple pieces of equipment may impact product quality. Examples include but are not limited to the following:

- a. Qualified (b) (4) limits are not accurately reflected in the equipment operating procedures.
- b. There are unresolved validation deviations for the (b) (4)

To address this concern, please establish operating parameters for your equipment based upon the capabilities as demonstrated during your equipment qualification. Please submit the pertinent manufacturing procedure or relevant section of the batch record to demonstrate the establishment of the equipment operating parameters.

5. Performance qualification data were not provided for the (b) (4). Please provide documentation and data demonstrating that the equipment is operating within the parameters specified in the batch production records. Information provided should include testing performed to demonstrate consistent product quality during the different purification steps; sampling plan(s) that summarize the methods used for sampling during production, and any non-conformances.
6. We are unable to evaluate your drug product visual inspection program. Please submit the following information for review:
 - a. Visual inspection results using the newly defined critical, major and minor categories, and AQL testing were not submitted for review. These visual inspection results should be performed using the new (b) (4)
 - b. Qualification documentation for the new (b) (4)
7. The (b) (4) which is adjacent to the (b) (4) where operators stand to perform manipulations and interventions during filling is incorrectly classified as Grade (b) (4) in-operation. Please revise this classification as Grade (b) (4) in-operation and submit the appropriate documentation demonstrating this classification. Please ensure that your environmental monitoring program and data from the repeated media fills adequately reflect this correction. Please submit the results of the environmental monitoring following the repeated media fills.
8. The Performance Qualification reports for (b) (4) (located in the (b) (4) and (b) (4)

(b) (4) (located in the (b) (4) , indicate testing failures for (b) (4) for both units, and moreover limits were exceeded for the maximum physical width for the former unit. Failure to provide (b) (4) could result in non-sterile product. Please provide a more detailed explanation of these failures. These units may require re-qualification upon further review based on your explanation.

9. The manufacturing process requires a (b) (4)-hour maximum duration from the time of drug substance (b) (4) to drug product filled vial freezer storage. However, based on batch records reviewed, this requirement is not tracked to insure the limit is not surpassed. The validation does not support a process duration longer than the (b) (4) hours. Please ensure this critical process parameter is adequately documented. Please provide documentation demonstrating this process time duration is met during production.
10. CBER requests that FKD Therapies Oy provide their calculations (not just the formula) used in determining the maximum valid (b) (4) method.
11. CBER accepts FKD Therapies Oy's proposal (provided in BL 125700/0.33 submitted on February 10, 2020) to reassess the (b) (4) release specification by the end of 2020 or after (b) (4) lots have been tested, to determine if a more stringent release specification is needed or if an addition of an alert limit to provide better tracking and trending of the quality control information for the manufacturing process is necessary. Please confirm that you will commit to this reassessment and subsequent action as needed.
12. The drug product (DP) shipping validation study submitted in the BLA is incomplete. Please submit shipping validation data to show that the DP can be shipped to the clinical sites and proposed commercial distribution sites without affecting product quality and container integrity and deviating from the recommended storage temperature.
13. You proposed to store the (b) (4) for up to (b) (4) and use the (b) (4) to initiate up to a maximum of (b) (4) commercial lots. Use of a stored (b) (4) to manufacture commercial drug product lots makes this a (b) (4). However, the supporting data on the quality and stability for the (b) (4) is incomplete. Please provide data to show that:
 - a. The (b) (4) are fully qualified as a (b) (4).
 - b. Evaluate if there is an expansion or generation of (b) (4)

- c. Conduct a comparability study to show that the DP manufactured using the (b) (4) is comparable to the DP used in the confirmatory clinical trials.
- d. Evaluate the stability of the (b) (4) for the intended storage period and submit the information in your complete response. Please note that the stability data should include an evaluation of the (b) (4) identity, purity and potency at the intended storage temperature and conditions. Sterility may be demonstrated through container closure integrity testing.
- e. Provide data for leachables and extractables testing for the (b) (4) storage containers, if different from previously provided information. Please note that the study for the leachables and extractables should be conducted using the product (b) (4)

14. The following lot release tests used to assess the quality of the DP are incomplete or require recalculations:

- a. You set an acceptance criterion for (b) (4) in the Drug Substance (DS) as (b) (4). However, the sensitivity of your test method does not support this acceptance limit. We note that the (b) (4) assay has a quantitation limit of (b) (4) and the assay requires the DS to be (b) (4) prior to performing the assay. Given this (b) (4), we believe the final result should be multiplied by (b) (4) to obtain the (b) (4) in the DS, thereby making (b) (4) the lower limit of detection for (b) (4). Please revise the acceptance criterion for (b) (4). Please submit a revised risk assessment for this new limit for (b) (4) in the DP and revise the justification for the allowable amount of (b) (4) in the drug product.
- b. We note the following calculation error for the presence of (b) (4) in the DP. Briefly, the calculation for (b) (4). While the calculation of (b) (4) in the DS is calculated assuming that all (b) (4) tests return a positive test result, the tests do not consistently provide this result. Therefore, it evidently makes (b) (4) to be the limit of detection for your test. Due to this error in calculation, the (b) (4) in the DS should be listed as less than (b) (4) rather than (b) (4) as proposed. Please revise the acceptance criterion for (b) (4). You must also conduct a risk assessment for this revised amount of (b) (4) in the DP and revise the justification for the acceptance criterion for (b) (4) in the DP.

- c. You have not evaluated the robustness of the (b) (4) assay used to quantitate the (b) (4) in the DP. Please evaluate the (b) (4) assay robustness with the DP that contains the novel Syn3 excipient.
15. The stability information for the DP is incomplete. You proposed a shelf life of 12 months for the DP; however, the stability data included in the BLA for the proposed commercial product (RTU formulation) is only for 9 months. Please provide updated stability information. Please note that the stability information should also include stability data to address the following outstanding issues:
 - a. Supporting data to show that the DP is stable when stored for 12 months. Please note that the stability evaluation should take into consideration the storage period for the DS to show that quality attributes of the DP are not compromised when the DS is stored initially for the proposed period of (b) (4) month prior to being formulated into the DP and stored for an additional 12 months.
 - b. You provided updated stability information to show that the novel excipient Syn3NODA is stable in the final formulation for a period of 12 months when stored at -60°C. However you have not provided data to show that the Syn3NODA is also stable when the drug product is stored at -20°C, the proposed storage temperature at the clinical site.
 - c. You have not yet validated the analytical method used to detect the presence of the functional excipient, Syn3NODA, in the DP. Analytical method validation is required to support the stability of Syn3NODA in the DP. Please provide the assay validation for the detection of the functional excipient, Syn3NODA, in the formulated DP.
16. In Module 3.2.P.2 you provided Summary Report CM-FKD003-SUM-15-035 entitled “In-use stability and compatibility study for rAd-IFN in (b) (4) in which you transferred the drug product from a 60 ml syringe, through urinary catheters, (b) (4) to mimic catheter administration into the bladder. Please address the following:
 - a. In Section 5.1.2 of the summary report, you describe the (b) (4) catheters that were used for this testing (i.e., (b) (4)).
(b) (4)
However, you did not provide information on the U.S. regulatory status of these catheters. Please provide information on the U.S. regulatory status of each of the (b) (4) catheters used in the compatibility study, including but not limited to whether the devices are U.S. FDA-cleared or -approved, the corresponding regulatory submission (e.g. 510(k) or PMA) numbers, and the cleared or approved indications for use.

- b. In your draft labeling in Module 1.14.1.3, submitted in Amendment 25 dated January 10, 2020, you state in Sections 2.2 Preparation and Handling and 2.3 Administration, that the drug product should be withdrawn from four (4) vials into a syringe(s) and instilled into the bladder using a urinary catheter. However, you did not include critical parameters for these delivery devices. Please propose critical device parameters (e.g., volume, material(s) of construction, French gauge, length, coatings, colorants, connector style, tip style, etc.) to include in the labeling in order to guide the clinician in selecting a syringe and urinary catheter that are compatible with your DP. While it is possible these parameters may include a range of selections/values (e.g., different materials of construction, different lengths, etc.), all proposed parameters and selections/values should be supported by compatibility testing and suitable for clinical delivery of the product. If there are any catheter types that should not be used with your product (e.g., in-dwelling catheters, catheters with antimicrobial coatings, etc.), please also include this information in the labeling. To support your proposed parameters and selections/values, please provide:
- i. a discussion of how each proposed parameter and selection/value is supported by your compatibility data.
 - ii. information regarding the catheters that were selected for use during your clinical studies, along with a summary of your clinical experience using these urethral catheters to deliver the DP (including any delivery-related adverse events) and how the catheters used in the clinical study compare to the catheters used in the compatibility testing and the proposed critical device parameters.

According to Section 2.2 Preparation and Handling of the draft label provided in Module 1.14.1.3, submitted in Amendment 25 dated January 10, 2020, the DP is transferred from the container closure into a syringe using a vented vial adapter. However, according to Section 3 Introduction of Summary Report CM-FKD003-SUM-15-035, the DP in the compatibility testing was first (b) (4) prior to withdrawal into syringes, (b) (4), and administration via catheter. It is not clear how the dose preparation steps described in the testing summary report represent the actual dose preparation instructions in the draft labeling or worst-case clinical dose preparation scenario. Please provide a comparison between the dose preparation steps used in the compatibility study and the proposed labeling and provide a rationale for why the compatibility test methods are adequately representative of the worst-case scenario for clinical dose preparation.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). 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 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. 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 the steps necessary for approval.

Please submit your meeting request as described in the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf>, and CBER's SOPP 8101.1 *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>.

We acknowledge receipt of your amendment(s) dated March 13, 2020, March 31, 2020, and April 15, 2020. Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross reference applicable sections of the amendment(s) dated March 13, 2020, March 31, 2020, and April 15, 2020 in your complete response to this letter and we will review those sections as a part of your complete response.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Zakaria Ganiyu at (240) 402-8329.

Sincerely,

Raj K. Puri, MD, PhD
Director
Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research