CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761126Orig1s000

OTHER ACTION LETTERS

BLA 761126

COMPLETE RESPONSE

Tanvex BioPharma USA, Inc.
Attention: Bonnie J. Mills, PhD
Vice-President, Clinical Development & Regulatory Affairs
2030 Main Street, Suite 600
Irvine, CA 92614

Dear Dr. Mills:

Please refer to your biologics license application (BLA) dated and received September 28, 2018, and your amendments, submitted under section 351(k) of the Public Health Service Act for TX01.

We acknowledge receipt of your amendment dated August 15, 2022, which constituted a complete response to our May 20, 2021, action 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.

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) manufacturing facility for this BLA, our field investigators conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

from labeling regulations and guidances. In addition, we encourage you to review the FDA guidance for industry *Labeling for Biosimilar Products*.

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 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.[3]

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, November 9, 2022, which addresses the proposed proprietary name, Nypozi. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.
- Present tabulations of the new safety data combined with the original BLA data.

[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

- Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

(3) Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.

(6) Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

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

(b) (4)

o address this risk, conduct a study evaluating the impact of the (b) (4). The assessment should include an evaluation of (b) (4) If the data support (b) (4) TX01 manufacturing process.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 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.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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 guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

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, contact Courtney Hamilton, Regulatory Project Manager at Courtney.Hamilton@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tanya Wroblewski, MD
Deputy Director (Acting)
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

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/

TANYA M WROBLEWSKI
02/14/2023 01:26:23 PM

BLA 761126

COMPLETE RESPONSE

Tanvex BioPharma USA, Inc.
Attention: Bonnie J. Mills, PhD
Vice-President, Clinical Development & Regulatory Affairs
2030 Main Street, Suite 600
Irvine, CA 92614

Dear Dr. Mills:

Please refer to your biologics license application (BLA), dated and received September 28, 2018, and your amendments, submitted under section 351(k) of the Public Health Service Act for TX01.

We acknowledge receipt of your amendment dated November 20, 2020, which constituted a complete response to our September 24, 2019, action letter.

We also acknowledge receipt of your amendment dated May 3, 2021, 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.

PRODUCT QUALITY

Facility Inspections

1. Following an evaluation of the last inspection performed at Tanvex BioPharma, Inc. (FEI: 3013021112) manufacturing facility at 10394 Pacific Center Court, San Diego, CA 92121 for this application, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the remaining objectionable conditions, and verification by the FDA, is required before this application may be approved.

   We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

2. During a recent inspection of the (b) (4) facility, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this BLA may be approved.

Comparative Analytical Assessment

3. The Agency's evaluation of the January 27, 2020, third party Analytical Similar Assessment Data Review Report identified several issues regarding data omission in the analysis of G-CSF receptor binding by SPR (b) (4) assay) as indicated in the March 15, 2021 Information Request (IR). Your March 19, 2021 IR response did not adequately address the following issues, impacting the reliability of the data provided to demonstrate that TX01 is highly similar to U.S.-licensed Neupogen:

(b) (4)

In addition, in Complete Response (CR) comment 2b in the CR letter dated September 24, 2019, issues were raised regarding data omission for the competitive binding ELISA assay. In the response to the March 15, 2021 IR, you provided a list of all the runs and samples that were excluded from the analysis. However, inadequate justification was provided for the exclusion of data with binding ratios (b) (4) and replicates that do not appear to be identical. Given the number of runs with binding ratios (b) (4) there is a concern that the method was not sufficiently qualified for its intended use.

Overall, these issues raise concerns regarding the quality of the data from G-CSF receptor binding analysis by SPR and competitive binding analysis by ELISA

submitted to support the comparative analytical assessment between TX01 and U.S.-licensed Neupogen. Therefore, at this time, there is insufficient information to make a determination that TX01 is highly similar to U.S.-licensed Neupogen notwithstanding minor differences in clinically inactive components. To address these issues, reliable data collected using binding assays that have been demonstrated to be fit for their intended use are needed to support the comparative evaluation of G-CSF receptor binding affinity between TX01 and U.S.-licensed Neupogen. The analysis should include lots of the proposed TX01 commercial material and TX01 lots used in the clinical studies. If TX01 lots from the clinical studies are not available, TX01 material representative of the clinical process may be acceptable with appropriate justification.

PRESCRIBING INFORMATION

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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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. In addition, we encourage you to review the FDA guidance for industry *Labeling for Biosimilar Products*.

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 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.[3]

CARTON AND CONTAINER LABELING

We acknowledge receipt of your proposed container label and carton labeling dated November 20, 2020. We reserve comment on the proposed container label and carton labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated February 12, 2021, which addresses the proposed proprietary name, NYPOZI. This name was found acceptable pending

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.

    - Present tabulations of the new safety data combined with the original BLA data.

    - Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.

6. Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

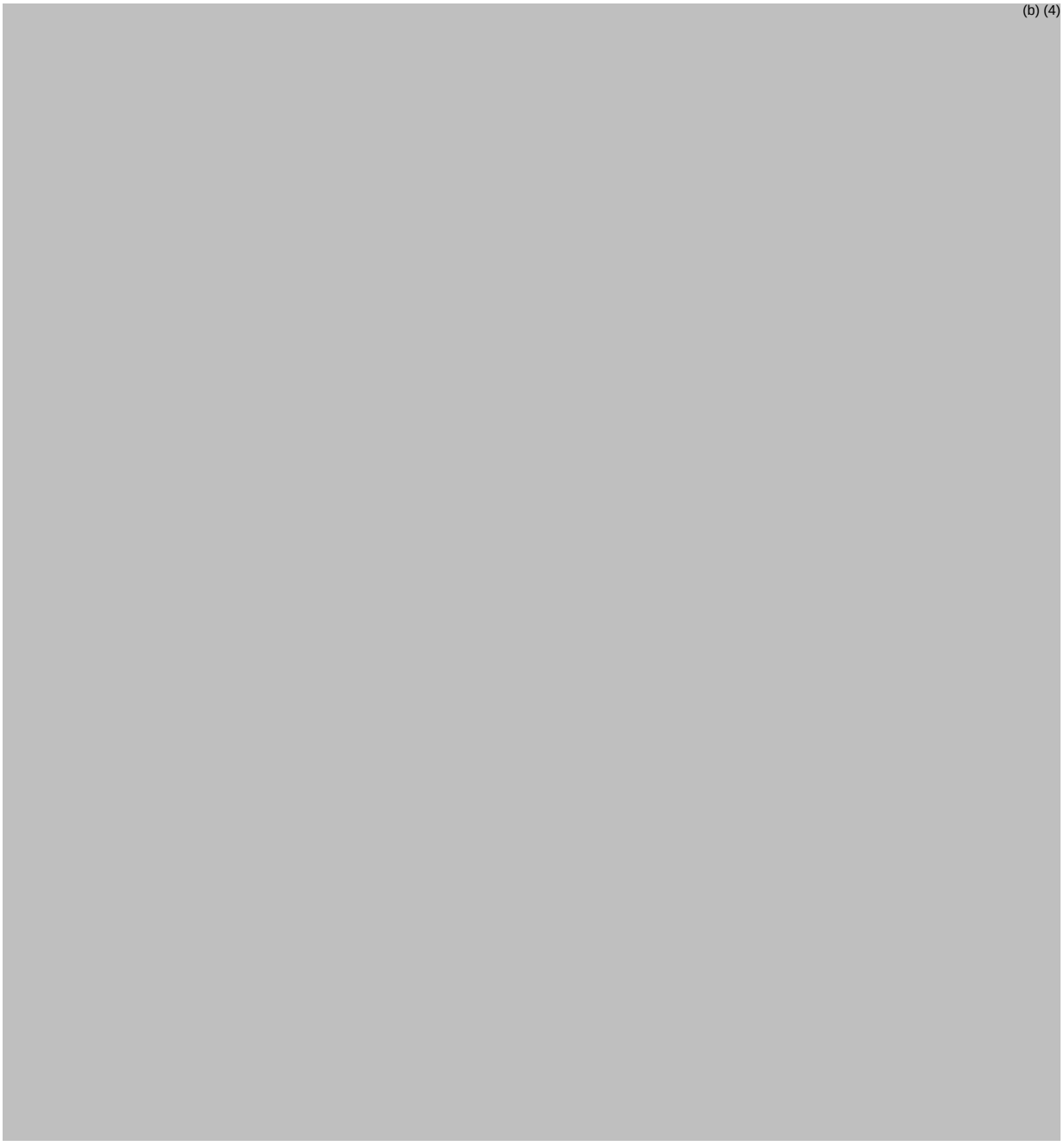
8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

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

Drug Substance

(b) (4)



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(b) (4)

Drug Substance and Drug Product Manufacturing

(b) (4)

Reference Standard

(b) (4)

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(b) (4)

Microbiology

19. Provide bioburden method qualification with three lots (b) (4) .

20. Provide a low endotoxin recovery study performed with two additional drug product lots.

21. Repeat the rabbit pyrogen test with the highest dose of TX01 drug product used in humans.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 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 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 guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

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, contact Brittany Garr-Colón, MPH, Regulatory Project Manager, at (301) 796-6153 or via email at Brittany.Garr-Colon@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

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/

ALBERT B DEISSEROTH
05/20/2021 07:26:23 PM

BLA 761126

COMPLETE RESPONSE

Tanvex BioPharma USA, Inc.
Attention: Bonnie J. Mills, PhD
Vice-President, Clinical Development & Regulatory Affairs
2030 Main Street
Suite 600
Irvine, CA 92614

Dear Dr. Mills:

Please refer to your biologics license application (BLA) dated September 28, 2018, received September 28, 2018, and your amendments, submitted under section 351(k) of the Public Health Service Act for TX01.

We acknowledge receipt of an amendment dated April 29, 2019 (Document Number 25), 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.

FACILITY INSPECTIONS

1. During a recent inspection of Tanvex, Inc. manufacturing facility (FEI: 3013021112) for this BLA, our field investigators conveyed deficiencies to the representatives of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRODUCT QUALITY

Comparative Analytical Assessment

2. During the April 23-May 2, 2019 inspection of the non-GMP laboratory at Tanvex, Inc. (FEI: 3013021112) that conducted most of the comparative analytical studies, several issues were raised regarding data analysis and management, and the suitability of the comparative analytical assays. These issues may negatively impact the reliability of the data provided to demonstrate that TX01 is highly similar to U.S.-licensed Neupogen. For example:

a. some of the assays used in the 2016 study were not qualified, and formal system suitability criteria were not in place at the time of use;
b. considerable issues were raised regarding documentation of data and omission of data from analysis for the competitive ELISA binding assay;
c. multiple changes were made to RP-HPLC data without documented justification, including deletion of an injection containing raw data as documented in the audit trail;
d. lack of documentation of the method procedures followed for determining the protein concentration of U.S-licensed Neupogen in the 2016 similarity study;
e. missing notebook record for analysis of TX01 and U.S.-licensed Neupogen by RP-HPLC during the 2016 similarity study; and
f. lack of written retesting procedures to manage “exceptional conditions”.

Overall, these issues raise concerns regarding the quality of the comparative analytical data submitted in your 351(k) BLA. Therefore, at this time, there is insufficient information to make a determination that TX01 is highly similar to U.S.-licensed Neupogen notwithstanding minor differences in clinically inactive components.

For the Agency to make an assessment of the application, it is critical that the data provided in your 351(k) BLA are reliable and complete. To address this deficiency, you will need to perform an appropriate retrospective review of all the comparative analytical data to ensure its reliability and completeness. The retrospective review is necessary to support a determination that TX01 is highly similar to U.S.-licensed Neupogen. This retrospective review may rely on your own internal audit or you may need to identify an appropriately qualified, external third party to perform an independent and thorough audit of all the comparative analytical sources and data used to support your 351(k) BLA for reliability and completeness. The Agency recommends that prior to initiating the internal or external third-party audit, the scope of the audit should be clearly pre-defined to address the items below. Although the Agency does not approve audit protocols, you may request the Agency to review your audit protocol design and content for comments prior to conducting the audit.

a. Purpose and scope of the audit,
b. A description of the qualifications and experience of the audit team members with regard to the intended purpose and scope of the audit,
c. Roles and responsibilities of the external third party and Tanvex, if applicable,
d. A description of how the external third party and Tanvex would address any disagreements or differences in opinion that may arise during the audit process, if applicable, and
e. A description of the nature and extent of information that will be included in the final audit report.

Depending on the final audit results, as appropriate, additional studies may be needed to generate new information and data to support the comparative analytical data in your

351(k) BLA resubmission. The Agency will not be able to perform a review of your 351(k) BLA until the final audit report provides assurance that all the comparative analytical information provided in the 351(k) BLA application is accurate, reliable, and complete.

3. Address the following regarding assessment of primary structure of TX01 and U.S.-licensed Neupogen using Glu-C Peptide Mapping with RP-HPLC-MS/MS:

   a. The peptide map data provided show differences in relative abundance of some peptide peaks between TX01 and U.S.-licensed Neupogen lots analyzed in the 2016 and 2018 comparative analytical studies. You attributed these differences to variability in experimental conditions between the 2016 and 2018 studies. However, differences are also observed in the peptide maps for TX01 and U.S.-licensed Neupogen lots analyzed within the same study in 2016 or in 2018. You did not address the differences observed in the TX01 and U.S.-licensed Neupogen data collected within the same study, such as the ratio of the G1:G1-dimer peaks. Explain the differences in peak intensity between TX01 and U.S.-licensed Neupogen lots analyzed within the same study, including whether sample preparation procedures may contribute to these differences. Provide data to support that the differences do not preclude a demonstration that TX01 and U.S.-licensed Neupogen have the same primary sequence.

   b. Table 4 of Section 3.2.R.3.2 shows the sequences of the minor peaks found in TX01 DP lot 17023. It is not clear whether the same minor peaks are found in U.S.-licensed Neupogen. Address whether the minor peaks reported in Table 4 are also found in U.S.-licensed Neupogen in similar levels and provide comparative data showing the abundance of these peaks in TX01 and U.S.-licensed Neupogen. If there are differences in the identity or level of these peaks between TX01 and U.S.-licensed Neupogen, justify why the differences do not preclude a demonstration that TX01 and U.S.-licensed Neupogen have the same primary sequence.

4. We note that the same Ellman's assay was used to assess free thiol content for the 2016 and 2018 studies (b) (4) Address how you determined that the assay used in the 2016 comparative analytical assessment was fit for intended use. This information is needed to support that the free thiol content results in TX01 and U.S.-licensed Neupogen are reliable and to support a demonstration that TX01 is highly similar to U.S.-licensed Neupogen.

5. Two comparative analytical studies were conducted, one in 2016 and a second study in 2018. During the inspection of the Tanvex Inc. facility (FEI: 3013021112)

where most of these studies were performed, you provided a summary of the history of changes to the analytical methods used in the two comparative analytical studies. The summary indicated that several of the methods used in the 2016 study were not qualified, and/or formal system suitability criteria were not established. Provide evidence that the non-qualified methods and those run without system suitability criteria as indicated in the inspection document "Summary of the History of Changes to the Methods and Reference Standards used for Analytical Similarity Assessment" were suitable for their intended use during the 2016 comparative analytical study.

6. You indicated that the CEX-HPLC method used for comparative analytical assessment is the same validated method used in the QC lab. Additional information is needed to assess whether the method was fit for its intended use in the comparative analytical studies. Specifically, the method was used to compare main peak, acidic species and basic species in TX01 and U.S.-licensed Neupogen. However, based on the information in reports# TR-2015-010-00 and SAN-VAL-0098 provided in the 351(k) BLA, the method was not validated for quantitation of basic species. In addition, while the method was validated for quantitation of the acidic species, in document SAN-DEV-0156 "Technical report for analytical characterization of TX01 and Neupogen on Charge Heterogeneity by CEX-HPLC" you mentioned that although the same assay was used for the 2016 and 2018 analyses, there were sensitivity differences in detection of low levels of acidic and basic species that resulted in slight differences in the integrated and reported levels of purity and impurities between the two studies. To support accuracy of the results for acidic and basic species in TX01 and U.S.-licensed Neupogen lots in each of the studies, provide data to support that the CEX-HPLC method is fit for quantifying basic species, and data and information to support consistent integration of both the acidic and basic species using CEX-HPLC.

Reference Standards

(b) (4)

(b) (4)

Drug Substance and Drug Product Manufacturing and Control Strategy

(b) (4)

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(b) (4)

Drug Substance Stability

(b) (4)

Drug Substance Microbiology

20. (b) (4)

Nonclinical

21. The animal data included in your application were obtained using prechange TX01, which was produced before a major manufacturing change to the to-be-marketed TX01. You have not provided adequate scientific justification for the relevance of the animal data generated with the prechange product to support a demonstration of biosimilarity of to-be-marketed TX01 to US-licensed Neupogen. Include one of the following in your resubmission: a justification for why animal studies are unnecessary in your application under section 351(k)(2)(A)(ii); an adequate scientific justification for the relevance of the animal data generated with the prechange product to support a demonstration of biosimilarity of to-be-marketed TX01 to US-

licensed Neupogen; or data from animal studies conducted using to-be-marketed TX01.

PRESCRIBING INFORMATION

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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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. In addition, we encourage you to review the guidance for industry "*Labeling for Biosimilar Products*" (July 2018).[3]

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 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.[4]

CARTON AND CONTAINER LABELING

We reserve comment on the draft carton and container labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, December 19, 2018 which addresses the proposed proprietary name, NYPOZI. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include new data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

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[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08415 9.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09330 7.htm
[3] https://www.fda.gov/media/96894/download
[4] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.

    - Present tabulations of the new safety data combined with the original BLA data.

    - Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.

6. Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

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

Clinical/Clinical Pharmacology

1. Although our review identified no issues with the design, conduct, data or analyses from Studies TX01-02, TX01-03 and TX01-04, please note that based on the observations described above under Product Quality that could have an impact on the product used in these clinical studies, the results from these studies cannot be

evaluated at this time with respect to whether these studies support a demonstration of biosimilarity.

Product Quality

Comparative Analytical Assessment

2. (b) (4)

Drug Substance and Drug Product Specifications

(b) (4)

Update all relevant sections of your 351(k) BLA with the correct information.

Reference Standards

(b) (4)

(b) (4)

Drug Substance Manufacture and Control Strategy

(b) (4)

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Analytical Procedures and Validation of Analytical Procedures

17. Validation report SAN-VAL-0111-00 for the cell proliferation potency assay indicates that this method is used for testing at Tanvex and "where appropriate, contract laboratories qualified by Tanvex Biopharma USA." Clarify whether in this original 351(k) BLA, in addition to Tanvex (FEI # 3013021112), you propose additional drug substance and drug product in-process, release, and stability testing sites (other than container closure testing). Note that additional testing sites should be supported by appropriate method transfer or method validation data.

Drug Substance Leachables

18. You conducted accelerated leachable studies for the drug substance container closure system. However, you did not provide leachable data for the drug substance container closure system at the end of the proposed shelf life under long-term storage conditions. In addition, you did not provide information about the assessment and control of potential leachables from the drug substance manufacturing process, (b) (4) (b) (4) used during the TX01 drug substance manufacturing. Provide leachables data from the TX01 drug substance container closure at the end of the shelf life. The leachable studies should also include an assessment of the impact of these leachables on product quality. In addition, provide a risk assessment and supporting data to address the potential leachables derived from the drug substance manufacturing process and their potential impact on product quality and patient safety.

Drug Product Quality

19. We reviewed your IR responses submitted on March 28, 2019 for the studies conducted to support compatibility of TX01 DP with the I.V. administration materials. The data provided are inadequate to support compatibility of TX01 DP with the administration materials for the reasons described below:

    a. To support chemical stability of TX01 DP used for I.V. administration, you assessed potency and particulate matter of the diluted DP. Your studies did not include assessment of all critical quality attributes of the product, such as purity, including high molecular aggregates. Provide data to demonstrate purity of the product with respect to size, charge, and hydrophobic variants. These studies may be conducted as part of the data requested in comment b(iv) below.

    b. You assessed potency of TX01 to support compatibility of TX01 DP with the I.V. infusion bags and infusion line. (b) (4)

[redacted] Address the following:

i. It is unclear whether the potency assay used in the compatibility studies was conducted within the validated parameters. [redacted] Therefore, it is unclear whether this variability is due to the performance of the assay or due to compatibility issues. Address the fitness of the potency assay used in the compatibility studies for intended use, including whether HSA has an effect on the performance of the assay. Provide information and data to support that the results reported in the compatibility study are precise and accurate.

ii. The potency acceptance criteria used to support the compatibility of TX01 with selected I.V. bags are [redacted]% relative potency. These acceptance criteria appear to be based on the drug product specifications using the previous potency assay with high method variability. The potency assay was revalidated with improved precision and the potency specifications were revised to [redacted]% relative potency to reflect the improvement in the performance of the potency assay. We note that several potency results in this I.V. compatibility study are between [redacted]%. Clarify and justify the acceptance criteria of [redacted]% relative potency used for the compatibility study. Your justification should include your rationale for why [redacted]% potency is adequate from the safety and efficacy perspective.

iii. Protein recovery should be assessed as part of the compatibility assessment to ensure adequate dosing. For samples containing HSA where HSA might interfere with the current protein concentration assay, you may consider a chromatography method such as an RP-HPLC assay for measuring protein recovery. To support the conclusions reached with the potency assay, provide data from the protein recovery studies. Alternatively, provide justification as to why the potency assay provides adequate assessment of recovery.

iv. Your data show that the potency of TX01 at [redacted]mcg/mL concentration is about [redacted]% in the [redacted] I.V. (polyvinyl chloride (PVC)) bag. We also note that variable potency values including low potency values of

[redacted]% are reported for the [redacted]mcg/mL concentration in the [redacted] I.V. bag. It is unclear whether these low recoveries as measured by the potency assay are adequate for I.V. administration. One possible approach to address this issue is to show that when using the same administration materials (i.e. PVC) and polyolefin intravenous bags, and [redacted] syringes), similar results are obtained for TX01 and U.S.-licensed Neupogen. The product attributes assessed in this study should include, purity, including aggregates, particulate matter (visible and sub-visible particles), protein recovery, and potency. If you pursue this approach provide these data to address this deficiency.

20. Assessment of leachables

    a. To support compatibility of TX01 with the prefilled syringe container closure system, you provided 27 months of leachables data for the [redacted] syringe and 15 months for the [redacted] syringe stored at the recommended storage condition of 2-8˚C and indicated that the studies in the [redacted] syringe are ongoing. You also provided 32 days of leachables data for the [redacted] syringe stored at 50°C, which you stated are representative of 24 months of leachables under the recommended storage condition of 2-8˚C. You stated that you considered the [redacted] syringe worst case scenario with respect to leachables because of its higher [redacted] content. To confirm compatibility of TX01 with the [redacted] syringe until the proposed expiry, provide updated leachables data for the [redacted] syringe stored up to the end of shelf life at the proposed long-term storage conditions.

    b. You did not provide information about the assessment and control of potential leachables from the drug product manufacturing process, [redacted] used during the TX01 DP manufacturing. To address this, provide a risk assessment and supporting data to address the potential impact of process- related leachables on product quality and patient safety.

21. To support the proposed [redacted] specification concentration ranges of polysorbate 80 (PS80) in the DP formulation, you provided stability data from formulation development studies under long term storage conditions for up to 12 months, 25^0 C for 6 months, and 40^0 C for 3 months and indicated that the formulation studies under long term storage conditions are ongoing. The data available under long term and accelerated storage show comparable DP stability over the proposed PS80 concentration range of [redacted]%. However, the data under stressed conditions suggest that [redacted] To support that the stability profile of DP formulated at the lower end, target, and upper end [redacted]

[redacted] release specification concentration range are comparable, update your application with the on-going formulation development study results under long term storage conditions.

22. Your application contains inconsistent information regarding classification of the following process parameters as critical (CPP), key (KPP) or non-key (NKP):

    a. The number of allowed [redacted] for TX01 drug substance is classified as KPP in the section 3.2.P.3.3.3, and as CPP in the section 3.2.P.2.3.6.

    b. You classified the [redacted] as NKP in section 3.2.P.3.5.3, and as KPP in section 3.2.P.3.3.4.

    c. The [redacted] is classified as KPP in section 3.2.P.3.3 and as CPP in section 3.2.P.3.5.

Clarify, with justification and data, the correct classifications for these parameters and update all sections of your application with the correct information.

23. The DP specification for volume of injection is "NLT [redacted] mL" for the 300 mcg PFS and "NLT [redacted] mL" for the 480 mcg PFS. Clarify the rounding rules used for volume for injection.

24. It is not clear whether release testing of TX01 DP is conducted on the final finished product after secondary packaging or on the prefilled syringe DP before secondary packaging. Clarify when release testing of TX01 drug product is conducted.

25. Based on the information provided in your 351(k) BLA, it appears that shipping validation for both bulk TX01 DP PFS and finished TX01 DP were performed using simulated shipping studies. If both validation studies are only based on simulated transport studies:

    a. Clarify whether the shipping containers and packaging configurations used in the simulated studies are representative of those you intend to use for commercial shipping.

    b. Because simulated shipping qualification studies may not adequately reflect commercial conditions, you should perform real time transport qualification studies for the finished drug product using commercial drug product and the mode(s) of transport, shipping containers and temperatures intended for commercial use. Provide real time transport qualification studies data for DP. Alternatively, you may provide a validation protocol for concurrent real time transport qualification of drug product.

Drug Product Device

26. On March 13, 2019, you provided volume of injection stability results of the PPQ lots for the 300 mcg/0.5 mL and 480 mcg/0.8 mL strengths of TX01 DP for 15 -16 months stability timepoint. Based on the provided data for volume of injection on (300 mcg/0.5 mL -16 months, 480 mcg/0.8 mL – 15 months), (b) (4) In your resubmission, provide the requested summary of data for volume of injection for the ongoing real time stability study of the proposed 24-month shelf life for both dose presentations (300 mcg/0.5 mL and 480 mcg/0.8 mL) of the PPQ lots to support your proposed shelf life of 24 months.

Drug Substance Microbiology

27. Endotoxin limits (b) (4) and should be (b) (4) based on your process capability.

28. Provide endotoxin specifications (b) (4) in section S.2.4 of the resubmission.

29. Include bioburden and endotoxin information from (b) (4) verification to assess microbial control (b) (4). Provide (b) (4) protocol in section S.2.5 of the resubmission.

30. Implement appropriate microbial controls for the receipt of new (b) (4) and update section S.2.5 in the resubmission.

31. Endotoxin release specification is reported in EU/mg. Provide endotoxin DS specification in EU/mL in section S.4.1 of the resubmission as this is a liquid product and the assay output is in EU/mL. Additional calculations and determinations must be performed for the conversion to EU/mg, which can introduce variability.

32. Provide the routine dilutions for the release and in-process endotoxin test methods in section S.4.2 of the resubmission. In addition, provide endotoxin qualification data from two additional batches of release and in-process samples in section S.4.3 of the resubmission. Data from in-process samples may be included in section S.2.4 of the resubmission.

33. Identify the batches used in the bioburden test method qualification of release and in-process samples as it is not clear whether the qualification was conducted using three batches or three samples of the same batch. Provide this information in section S.4.3 of the resubmission. Data from in-process sample may be included in section S.2.4 of the resubmission.

Drug Product Microbiology

34 (b) (4)

35. The (b) (4)-hour storage time of the diluted solution for intravenous infusion in the label is not supported by microbiology data. Bioburden in the infusion solution due to microbial ingress during the dilution process followed by long storage times is a safety concern as it may result in an infection. Provide microbiology data in support of the labeled (b) (4)-hour storage time in the resubmission. Alternatively, reduce the maximum storage time of the diluted solution to 4 hours.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 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 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.

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

BsUFA II APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for Original 351(k) BLAs under BsUFA II ('the Program'). The BsUFA II Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a BsUFA II applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential

with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Suria Yesmin, Senior Regulatory Project Manager, at 301-348-1725.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

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/

ALBERT B DEISSEROTH
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