



CBER REGULATORY REVIEW MEMORANDUM

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To Biologics License Application Submission Tracking Number # 125611/0

Subject BLA: Review of Bioburden, Sterility and Endotoxin Test Method Qualifications for Recombinant Coagulation Factor IX, pegylated (nonacog beta pegol)

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Applicant Novo Nordisk Inc. (Novo Nordisk)

Product Recombinant Coagulation Factor IX, pegylated (nonacog beta pegol)

Biologics License Application (BLA) Submission Tracking Number (STN) 125611/0

Submission Received by CBER 16 May, 2016

Review Completed 24 October, 2016

Material Reviewed

Method qualifications for: 1) bioburden; 2) sterility; and 3) endotoxin tests performed on nonacog beta pegol. In addition, information request response received 01 August, 27 September and 14 October of 2016 were reviewed.

Executive Summary

After a thorough review of this BLA, this reviewer finds the bioburden, sterility, and endotoxin test methods were qualified in accordance with (b) (4), respectively.

Background

On 16 May, 2016, Novo Nordisk submitted this BLA for nonacog beta pegol, a recombinant human factor IX, for use in adults and children with hemophilia B for control and prevention of bleeding episodes, perioperative management and routine prophylaxis.

Nonacog beta pegol is a sterile lyophilized powder manufactured in three different strengths of nonacog beta pegol protein; (b) (4) (500 IU/vial), (b) (4) (1000 IU/vial) and (b) (4) (2000 IU/vial). It is reconstituted in 10mM Histidine solution prior to intravenous injection. Nonacog beta pegol (b) (4) drug product (DP) are manufactured by Novo Nordisk, whereas the histidine solution is manufactured by (b) (4)

The DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews release specifications for microbial and endotoxin testing to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission: the confirmatory testing of submitted product samples; review of manufacturers' lot-release protocols to ensure biological products are released according to licensed test methods and product specifications. Therefore, this review will focus on the following method qualifications: Novo Nordisk's bioburden test and the sterility and endotoxin test methods performed at Novo Nordisk and (b) (4) to ensure the product matrix is suitable for these intended test methods.

Review

Bioburden Test Qualification for (b) (4)

Bioburden qualification tests (b) (4) qualifications) were performed on (b) (4) lots of nonacog beta pegol (b) (4) and three lots for total combined (b) (4) to demonstrate these matrixes do not inhibit bacterial and fungal growth. The test was performed according to (b) (4) using the (b) (4)

Testing involved (b) (4)

The recovery of CFUs in the presence of (b) (4) product did not differ by a factor (b) (4) from the value of their respective positive control. All microorganisms showed comparable growth between the test sample and their positive control. The test was performed and compliant with (b) (4) which indicated no inhibition of microorganism growth after the (b) (4).

Novo Nordisk submitted the bioburden results for several (b) (4) lots, which met their bioburden test alert specification of (b) (4). CBER finds their proposed release specification acceptable.

(b) (4) Method Qualification for (b) (4) DP
Novo Nordisk qualified their (b) (4) method for nonacog beta pegol (b) (4) DP to verify their product matrix was suitable for the intended test method in accordance with (b) (4)

Novo Nordisk performed a suitable test (b) (4) three lots of DP at 2000 IU/vial (b) (4). Based on the results, Novo Nordisk selected a test sample dilution of (b) (4) for their DP release testing, respectively. The maximum valid dilution (MVD) was calculated to be (b) (4) for DP where specification for endotoxin release specification (i.e., (b) (4) for DP) was divided by the lowest standard concentration of their kinetic standard curve (i.e., (b) (4)).

The inhibition/enhancement test was performed on three lots of (b) (4) three lots of DP at (b) (4) (i.e., lot numbers: (b) (4)). These lots were prepared at higher potency strength for test method qualification studies). The test sample was tested at (b) (4) for DP and all samples showed no inhibition or enhancement, as their (b) (4) recoveries for the positive product control (PPC) (b) (4) between (b) (4) for DP, which were within the acceptance criteria of (b) (4).

Novo Nordisk submitted the endotoxin results for several (b) (4) DP (at potency strength 500, 1000 and 2000 IU/vial) lots, which met their (b) (4) test specification of (b) (4) DP alert specification of (b) (4) and release specification of (b) (4). CBER finds these proposed specifications acceptable.

Sterility Test Qualification for DP

Novo Nordisk qualified their nonacog beta pegol DP matrix using the (b) (4) method by performing (b) (4) qualification studies on three lots at (b) (4) strength (i.e., lot number: (b) (4)). These lots were prepared at higher potency strength for test method qualification studies) and three lots at 2000 IU/vial strength (i.e., lot number: (b) (4)) to demonstrate the DP matrix is suitable for the intended test method. The test was performed using (b) (4) indicator microorganisms (i.e., (b) (4)).

The test for each microorganism was performed using (b) (4) of nonacog beta pegol DP that were reconstituted with (b) (4). For lots with 2000 IU/vials potency strength, one test sample vial was (b) (4).

This sample (b) (4) microorganism and its associated (b) (4).

After not more than (b) (4), all test media had (b) (4) comparable between the test sample and their respective PC control, while the NCs showed no growth. The test was performed and compliant with (b) (4) and the test results indicate there is no product inhibition on microorganism

growth; thus indicating the nonacog beta pegol DP matrix is suitable for testing via their (b) (4) sterility test method.

(b) (4) Method Qualification for Histidine Solution
 (b) (4) qualified their (b) (4) method for the histidine solution to verify its matrix was suitable for the intended test method in accordance with (b) (4)

The test was performed on three lots of histidine solution (i.e., lots (b) (4)). The test sample was tested at (b) (4). All dilutions (except (b) (4) sample for all lots and (b) (4) dilution for lot (b) (4)) showed no inhibition or enhancement as the (b) (4) recoveries for the PPC (b) (4), which were within the acceptance criteria of (b) (4). The MVD was calculated to be (b) (4) as calculated from the specification for histidine (b) (4) release specification (b) (4) divided by the lowest standard concentration of their kinetic standard curve (b) (4).

After evaluating (b) (4) concentration of excipients and components used in manufacturing of 10mM histidine solution, (b) (4) changed their (b) (4) release specification to (b) (4), which increased the MVD for release testing to (b) (4). CBER found this change acceptable since the PPC (b) (4) recoveries (between (b) (4) for proposed sample dilution of (b) (4) for release testing were within the acceptance criteria of (b) (4) submitted the (b) (4) results for several histidine solution lots, which met their (b) (4) specification of (b) (4). CBER finds their proposed release specification acceptable.

Sterility Test Qualification on Histidine Solution

(b) (4) qualified their histidine solution matrix using the (b) (4) method by performing (b) (4) qualification studies on three lots (i.e., lot number: (b) (4) to demonstrate the histidine matrix is suitable for the intended test method. The test was performed using (b) (4) indicator microorganisms (i.e., (b) (4) for all three lots and additional (b) (4) environmental isolates (b) (4)

The test for each microorganism was performed using (b) (4) syringes of lots (b) (4) of product each) and (b) (4) syringes of lot (b) (4) of product each) in either (b) (4). The test sample syringes were (b) (4)

After not more than (b) (4), all test media had (b) (4) comparable between the test sample and their respective PC control, while the NCs showed no growth. In case of (b) (4)

(b) (4), growth was detected in (b) (4), respectively. (b) (4) did not show growth in (b) (4) and test was repeated which was detected in (b) (4).

Even though environmental isolates demonstrated growth inhibition, they were recovered within the required (b) (4) in accordance with (b) (4). Because of CBER's experience with these microorganisms, we find this acceptable; thus indicating the histidine solution matrix is suitable for testing via their (b) (4) sterility test method.

Conclusions

After a thorough review of the information submitted in this BLA, this reviewer finds Novo Nordisk's nonacog beta pegol (b) (4) DP matrix are suitable for testing using their bioburden (b) (4) sterility and endotoxin test methods and the qualifications were performed in accordance with (b) (4), respectively. In addition, matrix for 10mM histidine solution is suitable for testing using their sterility and (b) (4) test methods and the qualification was performed in accordance with (b) (4), respectively. Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.