SAHPRA
South African
Health Products
Regulatory Authority

SAHPRA Head Office
Building A
Loftus Park
2nd Floor
Kirkness Road
Arcadia
0083

Enquiries: Biologicals@sahpra.org.za
Date 26/11/2021
Reference: AD (510879/80)

THE RESPONSIBLE PHARMACIST
SANOFI-AVENTIS SOUTH AFRICA (PTY) LTD
PRIVATE BAG X207
MIDRAND,
1685
E-mail: desiree.arthur@sanofi.com

Dear Sir/Madam

RE: APPLICATION FOR AMENDMENT: DUPIXENT AND DUBRANTIS- 510879 & 510880

After evaluation of the amendment dated 19 February 2021 sequence 0005 in terms of safety, quality and efficacy, SAHPRA recommend that; the following be approved:

1. Change to in-process tests ort limits applied during manufacturing of the active biological ingredient: Addition of a new test to monitor level of PLBD2
2. Change in the specifications used to release the final product- tightening of acceptance criterion. Addition of "safety system activated and lock" test for shelf life
3. Change in the specifications used to release the active biological substance. Inclusion of 5 additional tests (ID by peptide mapping, ID by iCIEF, glycan analysis, CHO protein content, CHO DNA content by PCR)
4. Change in the specifications used to release the active biological substance: tightening of the acceptance criterion for the Purity by CE-SDS (Reduced) and Purity by SE- UPLC specifications.

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5. Change to reference standard qualification protocol: tightening of Purity by CE-SDS (Reduced), Purity by SE- UPLC and Potency bioassay specifications relating to the working and primary reference material.
6. Change in the controls applied during the manufacturing process: tightening of in process limits of the Purity by CE-SDS (Reduced) and Purity by SE- UPLC
7. Change in the specifications used to release the final product: tightening of acceptance criterion
   of Purity by CE-SDS (Reduced) and Purity by SE- UPLC
8. Change in scale of the manufacturing process: introduction of seed train vessels and 2 additional bioreactors at Regeneron site,
9. Change to the active biological ingredient fermentation, viral propagation or cellular propagation process introducing a direct formulation process at Regeneron site
10. Change to in-process tests or limits applied during manufacture of the active biological ingredient, involving widening of the some of the approved limits as a consequence of the introduction of the direct formulation process
11. Addition of IOPS Raheen as an additional QC laboratory to execute numerous QC tests
12. Addition of IOPS Raheen, Ireland as an alternative API manufacturing site, quality control laboratory and storage site for the WCB of dupilumab FPP.
13. Proposal to add visually control during labelling
14. Change to an active biological ingredient manufacturing facility: Inclusion of Genzyme Geel as an alternative manufacturing facility and storage facility for the WCB
15. Inclusion of Genzyme Geel as an alternative QC testing sites for numerous tests
16. The use of the Sanofi Frankfurt site as a quality control testing site for numerous QC tests.
17. To add the Total Protein Content (SOLO VPE) test procedure for intermediates used in the manufacturing of dupilumab DS and FDS
18. Minor change to an approved analytical procedure (Rodent Parvovirus detection test)
19. Minor change to an approved analytical procedure (Identity by Peptide Mapping).
20. Minor change to an approved analytical procedure (Phospholipase B-LIE 2 content by ELISA)
21. The use of Sanofi Le-Trait to pack the bulk PFS with the soft needle shield.

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22. Change in the specifications used to release a primary container closure component or functional secondary container closure component
23. The minimum specification for the trim edge diameter is added for the West 1-3 mL Flurotec 4023/50G plunger stopper, while at the same time deleting the maximum specification of the same.
24. Change in the specifications used to release a primary container closure component or functional secondary container closure component: removal of details regarding the frequency of testing of incoming materials.
25. The use of new filling line using peristaltic pump technology.
26. Introduction of an alternative plunger stopper to the primary container closure of the bulk PFS at Sanofi sites.
27. Introduction of an alternative control for the syringe barrel lubrication test (automated control vs. current approved manual control).
28. To extend the QC testing regime of the already approved site, Eurofins Lancaster.
29. Inclusion of additional test, rodent parvovirus PCR to the test regime for RXM1J medium powder.
30. An additional pre-filtration step during final product manufacturing process.
31. The system suitability test criteria tightened for the container closure integrity test (CCIT).
32. Increase in the shelf life of the bulk PFS, final product (PFS) and final product PFS-S to 36 months when stored in the currently approved storage temperature.
33. To extend the QC testing regime of the already approved site, Irvine Pharmaceutical Services
34. Widening of the action limits of final cell viability due to the availability of expanded lot data.
35. Deletion of the lower action limit for total expansion time.
36. Change to in-process tests or limits applied during manufacture of the active biological ingredient: specifying the maximum reuse number/cycles of the TFF membrane.
37. Widening/updating the final cell density and initial cell density upper limits.
38. Widening of the charge variation analysis by iCIEF specification due to the discontinuation of the Protein Simple iCE280.

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39. To extend the shelf life of the drug substance and formulated drug substance to 36 months when stored at the currently approved storage temperature
40. Introduction of RSMAB668-9 and RSMAB668-10 primary and working reference standards .
41. Change to the cell banks: : the master cell bank will now be stored at ATCC in Gaithersburg, MD.
42. Widening of the chloride concentration specification pertaining to 10 N Sodium hydroxide due to the EU legislation changes.
43. Transfer of the QC testing activities for a non-pharmacopoeial assay to a new company Genzyme Waterford Ireland
44. Changes in the specifications used to release the final product involving addition of a test method 2 of the Ph.Eur bacterial endotoxin to be added as an alternative to method 1
45. Changes in the specifications used to release the final product involving addition of a test: method 2 of the Ph.Eur sterility test to be added as an alternative to method 1.
46. Changes in the specifications used to release the final product involving addition of a test: method 2 of the Ph.Eur bioburden test to be added as an alternative to method 1.
47. Changes to the holding times HT1, HT3 and HT 5
48. Extension of the time out of refrigeration – bulk product.
49. Change in the specifications used to release the final product: to combine the break loose and glide force test with the activation of safety system test for stability purpose
50. Change in the post approval stability protocol of the final product involving deletion of time points within the approved shelf life: removal of the T6 and T9 intervals and to optionally test at T18 and T30.
51. The adventitious virus in in-vitro test is moved from Wuxi Advanced Therapies, 4751 League Island Philadelphia, USA to WuXi Advance therapies 400 Rouse B, Philadelphia, USA.
52. Tightening of the system suitability criteria for the protein titer analysis by HPLC .

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53. IOPS Raheen is proposed as an alternative manufacturing facility and storage facility for the WCB.
54. To register IOPS Raheen, Pharmaceutical Product Development Inc, and Eurofins BioPharma Product Testing Munich GmbH. and BioReliance UK as new testing sites for biological methods.
55. Inclusion of Eurofins Ireland, Eurofins BioPharma Product Testing Munich GmbH, and BioReliance UK as additional QC testing laboratories
56. Option to directly formulate the API in Process Areas 6 and 7 as an alternative to the current formulation process that includes dispensing, freezing and storage of the API.
57. Editorial changes are noted.

Note 1: Change in the name and or address of a manufacturer from Irvine Pharmaceutical services to Nitto Avecia Pharma Services, Inc is noted and will be dealt with by the relevant unit within SAHPRA.

Note 2: Change in the name and address of a manufacturer from “Wuxi App Tech” to “WuXi Advanced” Therapies Inc is also noted

Yours faithfully

KHAMUSI MUTOTI

K.P MUTOTI
BIOLOGICAL MEDICINES UNIT MANAGER