

MEMORANDUM



Department of Health and Human Services
Public Health Service
United States Food and Drug Administration
Center for Biologics Evaluation and Research



From: Alexey Khrenov, PhD, Committee Chair and Product Reviewer
Laboratory of Hemostasis (LH), Division of Hematology
Research and Review (DHRR)/OBRR

To: Basil Golding, MD, Director, DHRR/OBRR

Subject: Designation of STN 125523/0.16 as a Major Amendment

DESIGNATION OF AMENDMENT 125523/0.16 AS MAJOR

Biologics License Application (BLA), STN 125523/0, for Fibrin Sealant, Human Fibrinogen Human Thrombin was submitted by ProFibrix BV (part of The Medicines Company) on 25 January 2014. The application is on a standard review schedule under the PDUFA V Program, with the action due date on 31 January 2015.

On 17 October 2014, ProFibrix submitted amendment STN 125523/0.16 containing responses to CMC questions regarding the specification of the drug product, which were conveyed to the company in an information request dated 10 September 2014 and during the Pre-License Inspection (PLI). On behalf of the review committee for the BLA under STN 125523/0, I recommend designation of STN 125523/0.16 as a Major Amendment.

JUSTIFICATION FOR MAJOR AMENDMENT DESIGNATION

SOPP 8402 and the PDUFA V Program define a Major Amendment as a submission of information to a pending application that extends the review clock. According to section V.D. of SOPP 8402, an amendment may be qualified as major when it contains a substantial amount of new manufacturing information and data not previously submitted to or reviewed by the Agency.

Amendment STN 125523/0.16 contains substantive revisions to sections 3.2.P.5.1 Specification and 3.2.P.5.6 Justification of Specification. The applicant basically provided a new Justification of Specification section for the drug product and raw materials. These documents include a significant amount of new data, and changes to product specifications based on statistical analysis of these new data.

Some of the changes proposed are not yet finalized and still under investigation. Their implementation will depend on the outcome of the investigations for out-of-specification results for several product assays. The investigations were initiated in response to observations made during the PLI and are planned to be completed by the end of November 2014. The investigations will likely involve additional method validation studies, which will generate additional new data. ProFibrix also committed to providing the response to another information request related to analytical method validation sent by

DBSQC by 26 November 2014.

Since amendment STN 125523/0.16 contains a substantial amount of new information and analysis (more than 200 pages), STN 125523/0.16 may be classified as a Major Amendment. In addition, this submission is also linked to future amendment(s) projected to be submitted to us close to the action due date. Also, on 24 October 2014, ProFibrix submitted amendments STN 125523/0.17, containing almost 500 pages of new documents related to stability studies and shipping validation; and STN 125523/0.18, containing datasets and analysis of clinical studies requested by the biostatistics reviewer.

NEW ACTION DUE DATE

According to section V.E.1.b of SOPP 8402 and the PDUFA V Program, a Major Amendment extends the action due date of an original application by three months. If the Major Amendment designation receives concurrence by the Director, Division of Hematology Research and Review, OBRR, the new action due date for BLA STN 125523/0 will be **30 April 2015**.