

From: [Tobin, Grainne A.](#)
To: [Ovanesov, Mikhail V.](#); [Gildner, Jean](#)
Cc: [Bhattacharyya, Lokesh](#); [Garnepudi, Varsha](#)
Subject: IR for STN 125586 Potency by TFPI Inhibition Assay
Date: Wednesday, November 01, 2017 2:35:49 PM
Attachments: [IR \(b\) \(4\) TFPI inhibition assay.docx](#)
[Additional Reagent IR for STN 125586-TFPI Inhib-final.docx](#)

Hi Mikhail and Jean,

Please find enclosed two sets of IR for the (b) (4) TFPI Inhibition Assay for STN 125586. One set is for the validation report and one set is to request more reagents as they did not send enough with the original shipment. Lokesh concurs with the IRs being sent to the sponsor.

Also, I am sorry but I will not be able to make tomorrow's meeting as (b) (6) (I forgot the meeting had been changed from today to tomorrow). I have no major issues with the resubmission. The (b) (4) TFPI Inhibition Assay, TME-0632 was well written and the validation report was carried out well. I have a few IRs pertaining to the specificity, (see above) but everything else was complete. I received samples and reagents etc for the insupport testing, however I need to request a bit more TFPI as they did not provide enough to enable method development and in-support testing (please see IR above). I should be able to complete the in-support testing by 24 November, and have the testing memo and final review memo completed by 1 December, provided nothing untoward comes back for the IR responses. The specification is a bit wide, but that seems to be a characteristic of their (b) (4) assays.

As for the work they have done on their reference standard and assigning a more relevant potency value, I have no issues with their new information.

I have updated Lokesh, so if there are any questions tomorrow, I am sure he will be able to address them.

If you have any further questions or comments, please let me

know. thanks, g

Sample and Reagent IR for STN 125586/o

We request that you provide us the following reagent for in-support testing of your BLA submission (STN: 125586)

(b) (4) TFPI Inhibition Assay

In the package of standards, reagents and test samples received from you on 17 October 2017, you provided (b) (4) of TFPI ((b) (4)). From the information provided in your SOP. TME-0632, this amount is insufficient to enable implementation and evaluation of the test method in our laboratory. Please provide (b) (4) of TFPI ((b) (4)).

Please ship the reagent to the address listed below:

Grainne Tobin
Center for Biological Evaluation and Research
Division of Biological Standards and Quality Control
10903 New Hampshire Avenue
WO75, G-634
Silver Spring, MD 20993-0002

Contact Grainne Tobin at 240-402-7424 and/or Varsha Garnepudi at 240-402-9547 for questions on the shipment.

We request that these samples, reagents and documentation be sent by 14 November 2017, or notify CBER by then when the shipment can be expected.

DBSQC Information Request for STN 125586/o

We have reviewed the following quality control assays for the drug product and their validation reports submitted under STN 125586/o.76, received on 4 August 2017 in response to the CR letter received by the sponsor on 17 August 2016, and have the following Information Requests. Please submit your response by 15 November 2017. If you are unable to do so, please provide us the time-line for submission of the requested information:

(b) (4) TFPI Inhibition Assay

Analytical Method Validation Report, MVR-0013, TME-0632, (b) (4) (b) (4) TFPI Inhibition Assay

- i. The composition of the (b) (4), described in Table 1 of the validation report, differs from the composition of (b) (4) described in Table 3.2.P.2.2.1 of section 3.2.P.2.2 Pharmaceutical Development, Drug Product. Please explain why different (b) (4) were used in drug product formulation and in method validation studies, and justify with data that the use of different (b) (4) did not affect the method validation results.
- ii. Please describe how the (b) (4) test sample used in the Specificity study is prepared.
- iii. The (b) (4) test sample gave a mean relative (b) (4) of (b) (4), while the controls and test samples ranged from (b) (4). Since the relative (b) (4) of the (b) (4) test sample are similar to the control and test sample results, please explain how these results demonstrate the method may be used to ascertain stability.