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In reply please refer to: P5-447-3/SC/AGM/1

Your reference:

Mrs Sheeba Manoj Nair
Head of QA
Semler Research Center Pvt Ltd (Otherwise known as JP Nagar site), 75A, 15th Cross, I Phase JP Nagar,
Bangalore, 560 078
Inde

12 April 2016

Dear Mrs Manoj Nair,

Prequalification Team – Inspection Services
Notice of Concern

In June 2008, the World Health Organization (WHO) Prequalification Team (PQT) implemented a Notice of Concern (NOC) procedure that is applied when an inspection is performed and serious observations are made that result in concern about the site's compliance with specified standards such as those relating to Good Manufacturing Practices (GMP) or Good Clinical Practices (GCP). This notice is issued in accordance with that procedure (see details on WHO-PQT website on this link: http://apps.who.int/prequal/assessment_inspect/info_inspection.htm#6.

WHO conducted inspections of your contract research organization (CRO) at Semler Research Center Pvt Ltd (Otherwise known as JP Nagar site) and at Semler Research Center Private Limited (Otherwise known as Sakar Nagar Clinical Unit), between 27 and 31 January 2015 and a follow-up between 2 and 5 December 2015 in order to verify compliance with Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) covering a number of studies, some of which are part of the dossiers submitted to PQT.

The inspections revealed critical and major deviations from GLP and GCP as published in WHO's publications (see references in the inspection reports). These deviations were presented to you during the inspections and listed in the copies of the Inspection Reports sent to Semler by email on 6 October 2015 and 11 February 2016, after the inspections.

Following the inspections, you were also sent a draft NOC by email on 12 February 2016. You were given an opportunity to submit an appeal, which was received on 25 February 2016. It was reviewed and discussed during an appeal committee meeting that took place in Copenhagen on 17 March 2016. You were also given an opportunity to provide supplementary documentation in response to the NOC after the appeal committee meeting. You provided a presentation, minutes of the meeting, as well as documents entitled "Trend analysis result interpretation for WHO studies" and "Trend analysis result interpretation for studies in the excel sheet identified by USFDA" on 21 March 2016.

Taking into consideration the findings of the inspection of 27 to 31 January 2015, your response to observations of that inspection, the findings of the follow-up inspection of 2 to 5 December 2015, your response to observations of that inspection, the assessment of the data provided after this inspection, including in appeal to the draft NOC on 25 February 2016, 17 March 2016 and 21 March 2016, I regret to inform you that certain deficiencies which are deviations from GLP and Good Clinical Practices (GCP) for several studies remain of concern.

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The specific issues that cause issuance of this letter are given below. They are not meant as a recapitulation of all inspection findings outlined in the inspection report and other subsequent reviews, which too must be resolved.

1. *With regards to data integrity:* On 2 December 2015 inspectors were provided with a copy of a spreadsheet file, that was found on your server, which upon careful review was observed to contain for specific studies either:

    a. an overview of manipulations of study samples, or
    b. instructions useful for the purpose of manipulating samples.

The spreadsheet lists the specific studies and details how specific samples (including subject numbers) can be or have been manipulated. In some cases the manipulation involved replacement of subject samples by samples from other subjects and where Test and Reference have been swapped.

These studies identified by the spreadsheet with Semler's internal study codes are:

S-11-299 (purportedly manipulated for Atazanavir)
S-12-547 or S-12-548 (Acetazolamide)
S-12-518 (Celecoxib)
S-11-273 (Saquinavir)

Upon investigation of the study documentation for these studies, inspectors identified evidence of such manipulation by comparing concentration-time curves for specific pairs of study subjects. The observations corroborate the manipulations described by the spreadsheet.

Furthermore, a similar type of manipulation has been verified in studies:

- HA549 (S-12-324) for Lamivudine

The study was used for a dossier submitted to PQT; the other studies listed above had other submission scopes.

Semler has acknowledged that "4 FDA studies and 1 WHO study have questionable data", that these trends "cannot be physiologically explainable" and that "there were system gaps identified during the retrospective investigative audit in the system due to which we are not able to identify who and why this happened". This implies that Semler acknowledges existence of these unnatural trends in their data, the root cause has not been identified and the system cannot support adequate root cause analysis for these issues of concern.

PQT is under the impression that these observations are an indicator of fraud, as they are consistent with interim statistical analysis followed by deliberate sample manipulation of remaining subject samples, when the point estimate at the interim analysis indicates the existence of product differences in terms of rate or extent of absorption, with the intention of bringing point estimates towards unity and thereby increasing the chances of proving bioequivalence.

Appendix 1 (confidential) shows one example from study S-12-324 where a subject's samples have been re-injected under the identity of another subject number and provides a listing of several examples where subject samples were switched. The curves are considered identical within the meaning of dilution and bioanalytical variation, and with Test and Reference swapped.

Manipulation of at least five studies over an extended period of time indicates this is a common practice; WHO is of the impression that to execute this type of manipulation several staff members on various levels within the organization have to be collaborating and coordinating. The issue is thus not confined to a single person operating outside of the quality management system.

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2. *With regards to the quality of chromatography and compliance with acceptance criteria:* Inspectors raised the problem with chromatographic quantification of study samples containing Artemether. Specifically, PQT requested re-integration of Artemether samples from studies MA112 (S-11-321), MA114 (S-11-306), MA110 (S-12-521), all of which were used for WHO submissions. PQT also asked for new PK/statistical analysis once the new chromatographic reviews had shown which subject needed to be removed due to the integration issues.

The new analysis of MA112 (a 2-treatment, 2-sequence, 2-period randomised study) was first submitted to PQT on 6 November 2015. It was considered unacceptable because the company reintegrated only the examples that were mentioned in the report, yet Semler had already been informed that the examples presented as bad or questionable chromatography was not a complete list. The re-integrated chromatograms were still excessively smoothed and of questionable shape and integration and they did not have the same appearance as chromatograms produced during the validation process. The company was given another opportunity during the inspection of 2 to 5 December 2015 to show inspectors an adequate re-integration of all chromatograms in the study. However this had to be redone yet again as it was still unacceptable. It was resubmitted to inspectors on 30 December 2015. 60 subjects were randomised and 18 subjects were excluded from the analysis due to dropout, withdrawal or chromatography issues. In the new statistical analysis, confidence intervals were reported with 44 degrees of freedom for the residual variability and this figure is not consistent with 42 subjects analysed. PQT could not reproduce the confidence intervals and therefore was not convinced that the new figures reported on 30 December 2015 as part of Semler's CAPAs/inspection response truly reflected product performance. Although corrected information was submitted in the appeal to this NOC, the fact that numerous errors had gone unnoticed by the company until pointed out by WHO, signals issues with the quality management system of the company. Since the company had been already given three opportunities to adequately perform integration and pharmacokinetic/statistical analyses, it is questionable whether WHO can fully rely on other data submitted by Semler.

It is noted that you stated, in your appeal, that Semler was following their SOPs on integration at the time, but this argument is not deemed valid as the company is expected to have SOPs in place that provide correct instructions on performing integration in a reliable manner and that the reasons for poor chromatography should have been investigated and resolved either at the validation stage or at the time of the performance of the bioanalytical part of the study.

In your appeal and during the appeal meeting that took place on 17 March 2016, you stated that the re-integrations did not have a significant impact on the studies submitted to WHO, except for study No. S-11-290 and CPL-427. For azithromycin HA617 (S-11-290), you admitted that the new integrations led to a failure to meet bioequivalence criteria but that MA099 (CPL-12-427) was still bioequivalent. Furthermore, the new Artemether integrations that you have submitted resulted in 15% of subjects being discarded in study S-12-521 and 10% in S-11-321. This is considered an acknowledgement on your part that there were poor chromatography practices that affected the accuracy of the data reported in the studies submitted to WHO.

Conclusion

The WHO Prequalification Team aims to make quality priority medicines available for the benefit of those in need. Medicines whose data is manipulated or otherwise associated with implausible evaluations are associated with unquantifiable risks due to unknown safety and efficacy and thus cannot be trusted to bring patients the desired level of benefit.

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The above problems observed at Semler and other problems described in the report, indicate the existence of a general or systematic deviation from commonly accepted quality standards, and cannot be ascribed to a single person or two working outside of the quality management system. On these grounds, PQT recommends an immediate stop for all submissions of dossiers relying in whole or in part on involvement from Semler until the underlying issues have been verified to have been adequately resolved.

The findings also bring into question the validity of the following studies performed for products that are under assessment (not yet prequalified):

1. HA651 (S-12-469) - fixed dose combination of Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 600mg/300mg/300mg
2. HA629 (S-13-586) - fixed dose combination of Lamivudine, Zidovudine and Nevirapine Tablets 150/300/200mg
3. HA617 (S-11-290) - Azithromycin Tablets 500mg
4. HA549 (S-12-324) - Efavirenz 600mg + Lamivudine 300mg + Tenofovir Disoproxil Fumarate 300mg Tablets
5. MA114 (S-11-306) - Artemether and Lumefantrine Tablets 20mg/120mg
6. MA112 (S-11-321) - Artemether and Lumefantrine Dispersible Tablets 20mg/120mg
7. MA110 (S-12-521) - Artemether and Lumefantrine Dispersible Tablets 20mg/120 mg
8. TB298 (S-14-830) - Rifampin, Isoniazid and Pyrazinamide Dispersible Tablets (75mg/50mg/150mg)
9. TB295 (S-14-813) - Rifampin and Isoniazid Dispersible Tablets 75mg/50mg
10. TB294 (S-14-790) - Ethambutol Hydrochloride and Isoniazid Tablets 400mg/150mg
11. TB275 (S-12-416) - Cycloserine Capsules USP 250mg
12. HA648 (S-14-967) - Abacavir Sulfate and Lamivudine Dispersible Tablets 120/60mg

The findings of this inspection also bring question to the validity of the studies performed for the following prequalified products:

- MA099 Artemether/Lumefantrine 20mg/120mg Tablets, Mylan Laboratories
- MA100 Artemether/Lumefantrine 40mg/240mg Tablets, Mylan Laboratories (supported by the study submitted for MA099 through comparative dissolution profiles)
- TB174 Isoniazid 300mg Tablets, Micro Labs Ltd
- TB195 Isoniazid/Rifampicin 150mg/150mg Tablets, Lupin Ltd
- TB196 Isoniazid 100mg Tablets, Lupin Ltd
- TB198 Ethambutol HCl/Isoniazid Tablets 400mg/150mg Tablets, Lupin Ltd

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- TB199 Ethambutol HCl/Isoniazid/Rifampicin 275mg/75mg/150mg, Lupin Ltd
- TB202 Isoniazid/Rifampicin 75mg/150mg, Strides Ltd
- TB207 Ethionamide 250mg Tablets, Lupin Ltd
- TB216 Ethambutol HCL/Isoniazid/Pyrazinamide/Rifampicin 275mg, Strides Ltd
- HA621 (HA467) Ritonavir Tablets 100mg of Mylan Laboratories.

For all of the above-mentioned dossiers submitted to WHO PQT, Applicants/sponsors are notified that risk assessments with proposed corrective and preventive action should be submitted for all of the studies at the earliest convenience (within 30 days for products that are already prequalified). Furthermore:

- For products that are under assessment: the assessment process will be halted until satisfactory corrective and preventive action is submitted by Applicants/sponsors. This is expected to include risk assessment with consideration for reformulation in the case of products where the study data could have been manipulated to conceal foreseeable failures to meet bioequivalence criteria, followed by the conduct of new bio-studies or the submission of bio-waivers, where applicable.

- For products that are prequalified: Applicants/sponsors are requested to submit bio-waivers, where applicable or new bioequivalence studies within the next 6 months, which may be extended to12 months on justified case by case basis depending on the grounds and criticality of the product. In the case of products where the study data could have been manipulated to conceal foreseeable failures to meet bioequivalence criteria, reformulation should be considered before proceeding with a bio-waiver or new BE study.

Publication of the Notice of Concern

Your attention is drawn to the World Health Assembly Resolution WHA57.14 "*Scaling up treatment and care within a coordinated and comprehensive response to HIV/AIDS*" of 22 May 2004, which among other actions, requests WHO:

"3.(4) to ensure that the prequalification review process and the results of inspection and assessment reports of the listed products, aside from proprietary and confidential information, are made publicly available;"

In accordance with the above resolution and the NOC procedure, if the CAPAs provided are unacceptable, we may proceed with immediate publication of this revised NOC. It should nevertheless be noted that, in this case, the nature of the observations is such that retrospective corrective action is not considered to be possible for the studies already conducted. You were given an initial version of this letter for review on 12 February 2016 and appealed on 25 February 2016. A meeting between WHO inspectors and assessors and Semler representatives took place on 17 March 2016. As a consequence of this meeting WHO agreed to downgrade the deficiency related to biochemistry/haematological data, but to retain the above two deficiencies related to data integrity and poor chromatography.

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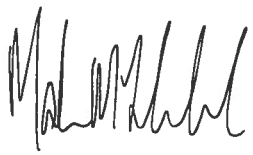
Please note that the NOC will remain active on the WHO-PQT website until satisfactory corrective actions have been submitted and verified by a follow-up inspection by WHO. As inspections of CROs within the WHO-PQ process are study specific, such a follow-up inspection will in addition need to be triggered by submission, to WHO, of a new study conducted after implementation of corrective and preventive actions.

Yours sincerely,



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