World Health Organization

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In reply please refer to: P5-447-3/DM/MM/SC

Your reference:

Dr Gayathri Sivakumar
Quest Life Sciences Pvt Ltd
SDF III, III floor
MEPZ, Tambaram
Chennai 600 045
Tamil Nadu
Inde

30 June 2015

Dear Dr Sivakumar,

Prequalification Team – Inspection Services
Notice of Concern

In June 2008 the World Health Organization's (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).

An inspection of your contract research organization (CRO) at Quest Life Sciences Pvt. Ltd, SDFIII, 3rd Floor, MEPZ, Tambaram, Chennai-600045, India, was conducted by inspectors from the WHO-PQT between 13 to 17 October 2014, focussing on Study No. LAZ/032/13, for HA619 Lamivudine, Zidovudine and Nevirapine dispersible tablets from Micro Labs Ltd. This inspection revealed critical and major deviations from the WHO Good Clinical Practices (GCP) and Good Laboratory Practices (GLP) standards as published in WHO publications. These deviations were presented to you in the Inspection Report prepared after the inspection.

Following the inspection, you were sent a copy of the Inspection Report by email on 26 March 2015, with a covering letter dated 23 March 2015. You were requested to respond to the observations listed in the Inspection Report within 30 days from the date of the letter. Your partial response received on 30 April 2015 has been received and evaluated. We regret to inform you that, after due consideration of the critical issues outlined in this report, a recommendation has been made for the study to be rejected and a Notice of Concern will be issued. Furthermore, please note that the nature of the observations was such that retrospective corrective action was not considered to be possible for the study under review, and corrective actions would be required only for the purposes of removing the NOC from the WHO website. The NOC would also be removed from the website if another sponsor, in the future, submitted in a dossier to WHO-PQT a study from your site that was accepted for inspection and found to be GCP/GLP Compliant.

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The following are details of the critical outstanding observations, together with our evaluation of your responses.

No.	Observation	Evaluation of response
1.	CRITICAL - With regards to failures in data integrity of clinical trial records, failures in the protection of subject safety, inadequate fulfilment of duties of the investigator, of quality assurance and other company staff, inadequate compliance to the protocol and procedures: For the LAZ/032/13 study, the majority of subject pre-study electrocardiograms (ECGs) (over 67%) were duplicates of each other. It is noted that subject details (e.g., subject identity number) and dates had been changed by the company, in the majority of cases, to make the ECGs appear as if they were from each of the different subjects who had participated in the study. In one instance, a single ECG was reused up to nine times for different subjects (e.g. the ECG for subjects 16, 28, 43, 45, 46, 47, 51, 52, 53, were identical.) This means that ECGs may not have been performed or were unreliable and therefore ineligible/unfit subjects could have been used in the study and protocol requirements may not have been met. *(Note: ECGs were sent to the WHO inspector post-inspection, in an email from Dr Gayathri Sivakumar, dated 23 October 2014, hence this observation is being given after the inspection.)*	Your response is considered unsatisfactory. You have not provided a suitable explanation, root cause investigation or corrective action for the duplicated ECGs. You stated that "*Nursing staff is not admitting that he has used the same ECGs. It is also possible according to him that the ECG machine could have a possible error in the digitalization and thereby the printing error could have happened*". This is not considered to be a sufficiently thorough investigation into the matter or explanation on how these problems were allowed to occur. We were also informed by other regulatory authorities covered within the scope of our confidentiality agreements, that similar issues were also found for their studies. Hence, these issues appear to be systemic in nature and occurring many times over a significant period of time, and not only as a one-time incident for the study submitted to WHO. Also, as stated in your response, these ECGs were taken under supervision of the Principal Investigator (or "CI"), which is of high concern to WHO and could potentially suggest that these compliance issues are performed under the supervision of senior management and hence may not be restricted just to ECGs. Furthermore, your proposal to submit ECGs taken post-inspection for the majority of the study participants, is not considered relevant because Period I was conducted from 08 October 2013 to 12 October 2013 and Period II from 29 October 2013 to 02 November 2013. This was more than one year ago and therefore the health status of the subjects may have since changed. ECGs should have been taken prospectively for each study subject in accordance with the protocol. Please note that we are deeply concerned that in your response, there was no clear acknowledgement that the ECGs had indeed been falsified. Given the serious nature of the falsifications of data identified by WHO inspectors, the action taken by your company is not considered sufficient on its own to prevent reoccurrence of such falsifications in this area or in other similar areas. .../...

2.	CRITICAL - With regards to records (clinical and bioanalytical): a. A number of forms relating to the LAZ-032-13 study were in process of being completed during the inspection as they had not been filled at the time of the activity. As inspectors entered the bioanalytical laboratory, laboratory staff members were seen in the process of completing records, some of them back-dated. An apparent attempt was made to hide documents from inspectors. Examples included, but were not limited to, the following: -Sample withdrawal/Restorage from Deep Freezerform, No. 000348, where Sample ID had not been completed for a sample recorded as withdrawn on 10 June 2014 – there was no identification of the sample taken although it had been marked as "withdrawn" from Rack II at 9:20 am and signed as done by the freezer custodian. The first sample was marked as being "for repeats". This was in process of being completed at the time of the inspection. Logbooks at the laboratory nevertheless provided sufficient traceability as to what had actually been done and enabled sufficient reconstruction of the study, but the fact that these were being backdated is a matter of concern. -Printouts of Chromatograms obtained on 13 December 2013 for method validation, were not signed off as having been checked. -Several blank forms were found in binders relevant to the study. Since these were not crossed out, the risk is that these had been left in to be filled after the fact. These documents should have been filled and/or returned to QA, since they were supposed to be controlled forms. These included: -Instrument identification SOP No. QLS-BA-002-11 Form No. 7, identified with a post-it note as "Cut-off and sign pending", Form No. 000127, which was completely blank. -Analytical run acceptance form SOP QLS-BA004-11, Form No. 61, No. 000231, which was partially filled, with	Although the corrective actions are partially acceptable, there is still no suitable explanation for so many blank forms in the binders that were found, or why staff members were found completing documents related to the LAZ/032/13 during the inspection in the first place.

	many blanks left in the table, No identification of the author or signatures whatsoever. -System suitability form SOP No. QLS-BA-007-06, No 14, Form No. 000683, which was left blank but found in the study binder. -Form No. 000669, for lamivudine standards, prepared on 13 December 2013 which was not signed off as having been checked. -Sample dilution form SOP QLS-BA-017-08, Form No. 72, Form No 00013, dated 13 December 2013, for pooled matrix batch ID MB-131/13-PM-01, not signed off as having been approved. -A handwritten sticky note was found in one of the binders in the bioanalytical laboratory stating: "LAZ/032/13 (ISR) LAZISR was started but not started" It was explained that incurred sample re-analysis (ISR) had been redone with revised concentrations for Nevirapine and Zidovudine. Since the sponsor had instructed them not to continue these studies, the related forms were only partially filled and the data was not submitted to WHO. b. Several clinical trial records were found in boxes (some covered in dust) in the Quality Assurance department. In one instance, a record containing original results of the breath analysis test on subjects for Study DIAK/052/14, signed and dated, was found crinkled in an empty unidentified box that appeared to be waste. When one of the employees present was asked about this document, he stated that it was going to be "cancelled" regardless of the fact that it contained raw data. There was no procedure for this. c. Adobe Acrobat Editor® was installed on computers in QA. This poses the risk of data being overwritten without traceability of the original record, reason for the change or of the author and date of the changes. [Note: this was originally given as a recommendation to the company but was later scaled-up to an observation because of the other data integrity issues noted at the company.]	

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As you have already been given an opportunity to respond to the issues raised in the inspection report, this NOC will be published without further notice.

Publication of the Notice of Concern

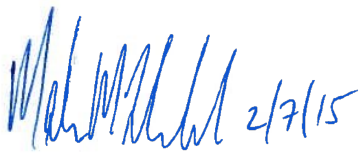
Your attention is drawn to the World Health Assembly Resolution WHA57.14 "*Scaling up treatment and care within a coordinated and comprehensive response to HIV/AIDS*" of 22 May 2004 which, among other actions, requests WHO:

"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, WHO will publish this NOC on its website since acceptable corrective actions have not been submitted. Please note that a NOC will remain active on the WHO-PQT website until satisfactory corrective actions (e.g., a new BE study) have been submitted and accepted by WHO.

Should you disagree with the reasons for issuing this NOC, you may email the details to which you disagree to prequal@who.int. Please quote "Attention: Coordinator, Prequalification Team" in the subject line. The matter will be investigated and unless advised otherwise, you can expect to receive a response within 15 working days. Should you not be satisfied with the response, you are advised to email the undersigned at prequal@who.int, quoting "Attention: Head RHT" in the subject line. All feedback will be treated in confidence and without prejudice.

Yours sincerely,



Dr Mark McDonald
Coordinator, Prequalification Team
Regulation of Medicines and other Health Technologies
Essential Medicines and Health Products