NOTICE OF CONCERN
Panexcell Clinical Lab Private Limited, Navi Mumbai, India

Notice of Concern (NOC) issued in terms of WHA57.14 read together with PQT Notice of Concern procedure of June 2008.

Your attention is invited 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*;"

Following the said resolution, the WHO Prequalification Unit (PQT) implemented (June 2008) a Notice of Concern procedure that is applied when concerns are identified about a site's compliance with specified standards such as those relating to Good Manufacturing Practices (GMP), Good Laboratory Practices (GLP) or Good Clinical Practices (GCP).

Based on these directives, the WHO Prequalification Unit hereby issues a Notice of Concern relating to the implementation status of Good Clinical Practices standards at **Panexcell Clinical Lab Private Limited, Navi Mumbai, India** to concerns on the CRO's quality management system and corresponding reliability in how the company carried out bioequivalence studies, which are regarded not sufficiently robust.

Kindly be advised that following the EMA publication of a *Referral under Article 31 of European Directive (2001/83/EC)*, the WHO Prequalification Unit initiated an investigation on the conduct of the bioequivalence studies by Panexcell Clinical Lab Private Limited relating to the WHO applications HA722, HA691 and HA731 submitted by the respective applicants; i.e. Emcure Pharmaceuticals Limited, Pune; Milan Laboratories (India) Pvt Ltd, Thane Maharashtra and Strides Pharma Science Limited, Karnataka, India.

Panexcell Clinical Lab Private Limited was requested by the PQT Inspection Team (PQT/INS) (5 June 2020) to submit a written response as to the assurance that the study data and study performance of the studies PCLPL-110-17 and PCLPL-147-15 related to the said WHO applications HA722 and HA691, were not compromised. Following review of the response, the following concerns remain:

1. The company failed to explicate how the duplicated profiles in the study inspected by the EMA-inspection Team changed the trend to make the study pass. Since non conformity observations on data integrity have been confirmed by the EMA, the WHO Inspection Team concerns remain whether the issue was only limited to that detected during the EMA inspection. In addition, as per the said EMA publication, samples from different patients were exceptionally similar and an instance of personnel documenting the wrong room temperature for the area where samples were being processed were identified. These findings read together with the WHO Inspection report (28 August 2018) raise serious concerns about the company's quality management system and the reliability of data from that site.
2. The company failed to adequately demonstrate the random distribution of PK parameter ratios for Dolutegravir molecule in study PCLPL-110-17. Trends / partial trends in group/subgroup have been identified by the PQT Unit. Providing the Cmax ratio A/B in log scale demonstrates that the probability of random distribution of data is very low, which is considered unusual.
3. The company failed to ensure the robust implementation and oversight of a quality management system to ensure that systematic procedures are in place to exclude any possible data manipulation or misrepresentation of data.

Seeing that the nature of the observations was such that retrospective corrective action was not considered to be possible for the studies under review, WHO/PQT has requested applicants of the affected products to review the impact of these findings and take actions to confirm bioequivalence of their products.

Kindly be advised that further corrective actions would be required by Panexcell Clinical Lab Private Limited only for the purposes of removing the NOC from the WHO website, and/or only if:

- the sponsors, Emcure Pharmaceuticals Limited, Milan Laboratories (India) Pvt Ltd or Strides Pharma Science Limited expressed the intention of submitting another study performed by your site to the WHO Prequalification Unit
- another sponsor, in the future, submitted a study from Panexcell Clinical Lab Private Limited in a dossier that was accepted for assessment
- until such time as the EMA publication in terms of the *Referral under Article 31 of European Directive(2001/83/EC)* is removed.

For further information please visit the WHO Prequalification Team - Medicines (PQT/MED) website at https://extranet.who.int/prequal or contact PQT directly at prequal@who.int

Mr Deus Mubangizi
Unit Head, WHO Prequalification Unit (PQT)

World Health Organization
Geneva, Switzerland
Email: prequal@who.int
Web: https://extranet.who.int/prequal