UPDATE: WHO position paper on Qinhuangdao Zizhu Pharmaceutical Co Ltd, Active Pharmaceutical Ingredient (API) Manufacturing Site following the issue of the USFDA import alert

Background

On 07 April 2017, WHO issued a position paper on the import alert placed on, Qinhuangdao Zizhu Pharmaceutical (QZP) by the United States Food and Drug Administration (USFDA) on 8 March 2017. This followed an inspection carried out by the USFDA at Qinhuangdao Zizhu Pharmaceutical, No. 10, Longhai Avenue, Economic Development Zone, Qinhuangdao, Hebei, China 066004 from 28 November to 01 December 2016. The inspection identified failures in the level of adherence to cGMP for APIs. In particular, the USFDA inspection team discovered serious breach of data integrity.

What has WHO done since issuing the position paper?

The WHO Prequalification Team (PQT) reviewed corrective and preventive actions (CAPAs) undertaken by the company and performed a for cause inspection at QZP in December 2017. The objective of this inspection was to verify the implementation of CAPAs undertaken by QZP as committed to USFDA.

The inspection revealed that efforts were made by QZP in addressing the USFDA observations in so far as it relates to:

- Training of staff, engagement of consultants and upgradation of the HPLC/GC systems, in particular the connection of all HPLC/GC to the company server and ensuring the availability of audit trails.
- Expanding on the comprehensiveness of batch manufacturing records to include cleaning certificates and analytical records (sample sequence table information).
- Changes to Management including new appointments.

In addition, the PQT inspection team noted that:

- Whereas the USFDA inspection was conducted in November-December 2016, the QZP timelines for completion of some of the CAPAs e.g. review of integrity of data of batches shipped to the rest of the world (other than US); review of all test records and chromatograms; and review of batch records and supporting documents for data integrity were unrealistically long expanding to June - December 2018.
- The new Management had not pronounced on any strategy related to prevention of data manipulation. Reliance is on detection measures rather than preventive (prospective) measures. Over reliance on reviews of audit trails was identified with no measures undertaken in improving attitude of staff towards data integrity.

1 https://extranet.who.int/prequal/sites/default/files/documents/PositionPaper_QinhuangdaoApril2017_0.pdf
• There were no records on rehabilitation of staff associated with the identified data manipulation with the staff member still involved in critical laboratory functions and decision making.

• The policy for privileges was irrationally given to chemists. This practice cannot rule out potential data manipulation or modification to parameters without appropriate supervisory oversight.

• Review of the electronic data, revealed that different HPLC processing methods were used for the same test e.g. blank, standard, diluted standard, sample solution of related substance test – the processing methods used were often different from those specified in the authorized/validated procedures.

Following the inspection and receipt of the WHO-PQT inspection report, QZP submitted a CAPA plan which was reviewed. The CAPA was found to be acceptable however an on-site verification inspection to confirm the satisfactory implementation is required. A WHO-PQT follow-up inspection is planned for October 2018.

WHO action and advice

WHO PQT has prequalified two finished pharmaceutical products (FPP) for which the inspected QZP is listed as the API supplier for Levonorgestrel. In addition, WHO has also prequalified the two APIs i.e. Mifepristone and Ethinylestradiol manufactured by QZP.

To date, WHO PQT has not received any reports or complaints from the market relating to the quality of Levonorgestrel tablets. Never-the-less, FPP manufacturers of prequalified products that use Levonorgestrel manufactured by QZP are requested to take additional measures to ensure that the quality of all batches of Levonorgestrel is assurred. In addition, seeing that there is currently no alternative WHO-PQT prequalified Levonorgestrel API, the WHO-PQT is working closely with the FPP manufacturers to identify additional sources for Levonorgestrel.

Until further notice, in view of the noted improvements, and the acceptable CAPA plan to address the outstanding deficiencies identified in the last inspection, procurement agencies may continue to procure FPPs that contain API produced at QZP. WHO-PQT intends to conduct an on-site follow-up inspection of QZP by October 2018 and will provide further updates.

The prequalification status of Qinhuangdao Zizhu Pharmaceutical Co Ltd prequalified APIs (Levonorgestrel, Mifepristone and Ethinylestradiol) remains unchanged.