World Health Organization

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

Your reference:

Mr Pritam Wade
Regulatory Affairs
Themis Medicare Limited
Plot No 69-A
GIDC, Vapi, Gujarat
India

8 June 2011

Dear Mr Wade,

Prequalification of Medicines Programme
Notice of Concern

In June 2008 the WHO Prequalification of Medicines Programme implemented a Notice of Concern 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 this procedure.

An inspection of your pharmaceutical product manufacturing facility at Themis Medicare Limited, Plot No 69-A GIDC, Vapi, Gujarat was conducted by inspectors from the WHO Prequalification of Medicines Programme on 11-14 April 2011. This inspection revealed several critical and major deviations from the World Health Organization Good Manufacturing Practices standards as published in WHO publications. These deviations were presented to you during the inspection and listed in the Inspection Report prepared after the inspection.

Following the inspection, you were sent a copy of the Inspection Report by email on 26 April 2011. In addition, a Notice of Concern (NOC) was emailed to you dated 29 April 2011. You were requested to respond to the observations listed in the Inspection Report as well as in the NOC within 30 days from the date of the letter. You have provided us with corrective and preventive actions on 25 May 2011. Your response has been evaluated and there are some observations that are of concern, in particular the response provided on the critical and major observations which were found inadequately addressing the observations. They are detailed below:

1. The company failed to appropriately implement a quality management system addressing deviations. [***Reference: Annex 2, WHO GMP for active pharmaceutical ingredients, clause 2.16, 2.17.***] For example, the planned deviation report for [redacted]) was reviewed and found inadequate. Examples of the inadequacy include but are not limited to the following:
   i. The optimization of process parameters was carried out in Oct 2010 to achieve [redacted] content less than 1.0% to meet customer and pharmacopoeial requirement. 5 batches were manufactured using process parameters provided by the R&D. However, all these batches failed in [redacted] and yield was found less than the standard yield.

.../...

ii. Product Quality Review (PQR) stated that at least 99 batches were made under this deviation. Data was reported on 81, most of which failed, indicating that the process was not validated.

iii. It was stated in the deviation report that further batches can be continued under deviation to optimise the process parameters. Most of these batches didn't comply with Ph Eur (EP) specification ([redacted]) but released for sale according to USP 32.

iv. There was no provision made in the SOP on Handling of Deviation ([redacted]) to carry on with manufacturing of further batches in spite of failing in [redacted].

Response to this observation was found deficient as no corrective action or any other documentary evidence was provided to indicate how this observation was addressed by the company.

2. The company failed to appropriately ensure the quality of key materials (including starting materials) before being used in the manufacturing of [redacted] [*Reference: Annex 2, WHO GMP for active pharmaceutical ingredients, clause 2.17*]. The starting material ([redacted]) was manufactured in-house in block 11A and released for use without testing. Also, block 11A, where [redacted] was manufactured, was unacceptable in that,

   i. The equipment used to make [redacted] was unacceptable, both in design and standards of housekeeping and maintenance.

   ii. No QC testing was done on [redacted], the key material for the separation of the enantiomers in [redacted].

   iii. Specification ([redacted]) for [redacted], effective date 1 August 2008, did exist for this material. A review was required in July 2010 but this was never conducted. It was confirmed from the QC lab that samples of [redacted] were never sent for testing.

Response to this observation was found deficient as no corrective action or any other documentary evidence was provided to indicate how this observation was addressed by the company. In addition, copies of new specifications of reactors and open tanks were not provided.

3. The company failed to maintain block 5, centrifuge [redacted] in an appropriate state of repair [*Reference: Annex 2, WHO GMP for active pharmaceutical ingredients, clause 4.10 and 8.51.*] due to the fact that:

   i. There were fibres seen on the pipe feeding the washing nozzles.

   ii. The suspension feed pipe had evidence of corrosion.

   iii. On the side of the centrifuge lid, patches of rust were seen.

It is further noted that a complaint (market complaint No: [redacted]) was received from the customer on the black particles in the finished product.

Response to this observation was found deficient as no corrective action or any other documentary evidence was provided to indicate how this observation was addressed by the company. For example, no photographic evidence was provided and no assignable cause was determined to minimize or stop such occurrence in future.

4. The company failed to adequately control laboratory operations [*Reference: Annex 2, WHO GMP for active pharmaceutical ingredients, clause 11.10*]. Examples include but are not limited to the following:

   i. Quality control lab reports directly to plant head instead of quality assurance department, although this was unclear, whereas the common arrangement is for QC to report to QA or both to be in one unit.

.../...

ii. Various key procedures were not available to ensure adequate control on lab activities. In particular, there was no SOP available on the level of access rights given to lab personnel for method parameters. It was noted that QC executive was given authority to amend integration parameters and given training.

iii. Specifications of key starting materials (in-house) were not scientifically sound and appropriate to ensure starting materials conform to established standard of quality, in particular [redacted].

iv. In-house working standards were prepared without confirming the level of impurities and solvents present.

Response to this observation was found deficient as no corrective action or any other documentary evidence such as SOPs and associated records were provided.

5. The quality management system was not appropriately maintained. PQR for year 2010 was reviewed and found inadequate. [***Reference: Annex 2, WHO GMP for active pharmaceutical ingredients, clause 2.50 and 12.6***]. Examples include but are not limited to the following:

i. PQR for [redacted] didn't include changes made in the manufacturing process. Also, review of deviations, self inspection, related substances test, residual solvents etc were not included in the APR.

ii. Total 657 batches were manufactured in 2010. Out of these 657 batches, 222 batches were of 88 kg on [redacted] input basis and 435 batches were of 80 kg on [redacted] input basis (output 165kg).

iii. Yield range was wide and output of batches varied from 155 to 196 kg for 88 kg in put batch size and from 126 to 168 kg for 80 kg in put batch size. Process was modified in December 2010 to get the [redacted] content below 1%.

iv. 99 deviations were taken under deviation to optimize the cooling time to get the [redacted] content below 1.0%. However, under the list of deviation recorded during the year 2010 for APR, only 4 deviations were recorded ([redacted] to [redacted]).

v. Cpk value for output of [redacted] was reported 0.34 and there was no specification defined for the Cpk. Moreover, Cpk values of Jan 2010 for pH, SOR, MP, SA, LOD and Assay were reported as 8.04, 2.07, 2.9, 0.87, 2.70, 2.70, 2.08 and 3.90 respectively.

vi. Critical quality attributes were trended on monthly basis due to the high number of batches manufactured in 2010. However, monthly trended data were not transcribed to annual data. Also, critical parameters such as pH, specific optical rotation, SOR, melting point, sulphated ash, LOD and Assay were trended instead of key parameters such as related substances and residual solvents which should also be trended.

vii. For 80 kg [redacted] input, the output specification set was 165+/-10% (155 to 175kg), while for 88 kg, output specification set in the batch manufacturing record was 181+/-10% (163-199kg). It has been seen from the APR output review that output was reported less than 163 kg for many batches ([redacted]) against their pre-defined output limit of 163 to 199 kg. However, no appropriate action was initiated.

viii. Rejected finished product [redacted] (Batch No [redacted]) was not included for annual review.

Response to this observation was found deficient as no corrective action or any other documentary evidence was provided to indicate how this observation was addressed by the company.

Please provide a further detailed response to the above observations, including supportive documentation reflecting corrective actions taken, or planned to be taken, by the company. Your response should reach this office within 30 days from the date of this notice. Please ensure that your response is comprehensive and clearly addresses, in detail, all of the issues raised above.

WHO may withhold prequalification of all new products containing an API manufactured at this site until these observations have been satisfactorily addressed and WHO has verified and confirmed the acceptability of the corrective actions. In addition, if these observations are not corrected within a reasonable timeframe, WHO may consider suspension of the product listed as prequalified from containing an API from this manufacturing site, and/or may recommend suspension of procurement of all prequalified products containing an API manufactured at this site.

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 Notice of Concern procedure, the WHO will now publish this Notice of Concern on it's website. Please note that a Notice of Concern will remain active on the WHO Prequalification of Medicines Programme website until satisfactory corrective actions have been submitted and accepted by the WHO.

Yours sincerely,

Mr Anthony Gould
Manager
Prequalification of Medicines Programme
Quality Assurance and Safety: Medicines