World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Tel. direct: +41 22 791 22 46
Fax direct: +41 22 791 47 30
E-mail : prequalinspection@who.int

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

Your reference:

Mrs Gauri Sapte
Business development Director
Svizera Labs Private Limited
Plot D 16/6
TTC Industrial Area MIDC
Turbhe, Navi
Mumbai 400703
Inde

2 September 2015

Dear Mrs Sapte,

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.

An inspection of your pharmaceutical product manufacturing facility at Plot D 16/6, TTC Industrial Area, MIDC, Turbhe, Navi, Mumbai – 400703, India was conducted by inspectors from the WHO Prequalification Team from 4 to 7 June 2015. This inspection revealed several critical and major deviations from the WHO GMP standards as published in WHO publications. These deviations were presented to you during the inspection in the most part 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 8 July 2015. Due to the seriousness of the deficiencies being raised, you were requested to respond to the observations listed in the inspection report within 15 days from the date of the letter. You submitted an appeal to WHO on 9 July 2015 to the NOC, and a response was provided to you by email on 9 July 2015. On 13 July 2015, you were also sent a Notice of Concern letter. You responded to the inspection report, and to the Notice of Concern letter on 23 July 2015 and on 3 August 2015. The following describes the critical and major observations that remain of particular concern as well as your responses and the results of our review of all of the information submitted up to date:

.../...

1. *The company failed to adequately perform dissolution tests and may have manipulated dissolution test results. Namely:*

a) As part of the investigations on concerns about the integrity of dissolution results, the laboratory was requested to perform, under observation, the dissolution tests for the TB 193 Rifampicin 150 mg/ Isoniazid 75 mg/Ethambutol HCl 275 mg/Pyrazinamide 400 mg Tablets (Prequalified, referred to as the 4 FDC in the report), on a stability sample for the time-point of 18 months (30 °C/75% RH blister), batch No. SL2231.

During the first test, one of the solution vials inside the auto-injector was switched, without notifying inspectors of what was being done. Further to questions from inspectors, the switched vial was explained, on the next day, to be the bracketing solution. The laboratory claimed that the original bracketing solution vial was switched with another bracketing solution vial that had been stored in the refrigerator to avoid issues related to the stability of rifampicin. However, after injection, the refrigerated bracketing solution did not fall within system suitability acceptance criteria (2.396% RSD) and the run was rejected by the company. Dissolution results were of 89.03, 87.50, 81.12, 78.72, 80.55, 86.68% and therefore did not comply with S1 criteria of the approved WHO specifications of NLT 75% (Q) in 45 minutes at 100 rpm. The run was restarted overnight in absence of the inspectors and passing dissolution results, over 90% for each tablet tested were obtained. The inspectors requested that the dissolution test be repeated, in front of them on 7 June 2015. Results of 84.21, 85.60, 88.07, 89.50, 89.79 and 90.31% were obtained, which differed from the results obtained by the laboratory in the absence of inspectors. The original bracketing solution was also retested and was within acceptable system suitability limits hence it is not clear why it was switched – no stability period or the necessity to store the standard under refrigeration was specified in the company's analytical method. Most importantly, no acceptable explanation for these differences in test results could be found, and such low results had not been reported in the past – these were outside normal trends reported by the company over the previous years of manufacturing (2014 and 2015) in the product quality reviews. It therefore appears likely that dissolution tests results were being manipulated to appear higher than their actual values.

The corrective and preventive actions described in your response, consisted of installing and qualifying one new dissolution tester. This response is inadequate because it does not address the inability of your current quality management system to detect and prevent intentional and biased influencing of dissolution testing results. The issues of training and personnel qualification, for instance, are still not addressed. Moreover, you have yet to provide a suitable explanation as to why the run passed the initial system suitability tests but not the final bracketing system suitability or why the original final bracketing solution was replaced with a different solution during the ongoing analysis. Your explanations that the dissolution test results may have been affected by calibration, which consisted of measuring the temperature of the bath and vessels during the test, is not substantiated by adequate evidence either. Your statement that the deviation between the results obtained in the absence of inspectors on the evening of 5 June 2015 are within the normal acceptable range is debatable and was not supported by any statistical calculations or scientific evidence.

b) Records were not adequately taken at the time of the performance of dissolution tests. During the observed repeats of the SL2231 dissolution test, the different vessels were not systematically numbered and no observations were taken on the results (e.g., if there were partially undissolved tablets or deposit at the bottom at the time of performing the test). Further to inspector comments, the laboratory brought in a laboratory notebook where preparation data would be recorded – this still did not include exact details of when the test was started and of the time of addition of tablets to each vessel, and of the observations on the tablets. The time of withdrawal of each sample was not recorded either.

.../...

The corrective and preventive actions described in your response, consisted of installing and qualifying one new dissolution tester that has the ability to electronically record and print some of the parameters of the tests being performed. This response is inadequate because it does not fully address laboratory personnel's inability to adequately follow instructions or to document actions being performed in a timely manner in general. Furthermore, it does not address the inability of your current quality management system to detect and prevent poor practices in the first place.

c) Only a single 10 ml volumetric pipette was used in the laboratory and was used to take the six dissolution samples – there were not enough pipettes on hand to have six dry pipettes readily available to take samples on a timely basis.

In your response, you provided an inventory record dated 14 July 2015, listing 15 pipettes of 10 ml. During the inspection, both inspectors individually requested to see all available pipettes and only one of each kind was shown and your record, which is dated after the inspection, does not demonstrate that there were more than enough pipettes to withdraw six samples on a timely basis. In any case, the analyst performing the dissolution tests also confirmed twice that he routinely usually used only 1 pipette to withdraw the six dissolution samples. There is therefore no evidence that an adequate number of pipettes for use during dissolution testing was available which further puts into question the reliability of the dissolution. The response has not adequately addressed these concerns.

d) (Point e of the original NOC) Samples taken were not filtered immediately – this step took approximately 15 minutes (Whatman™ paper filters were added on top of test tubes to perform filtration of dissolution samples). Since this delay would have allowed dissolution to continue for 15 minutes, the actual dissolution time-point in the specifications could not be respected for the tests done in this laboratory.

The installation and qualification of one new dissolution tester with in-line filters, post-inspection, is acceptable because it will help ensure that filtration is performed immediately on this instrument, it does not address the inability of your current quality management system to detect and prevent poor practices in the first place and does not address the validity of the tests that were performed up to date. Also, the statement provided that "As very small amounts of powder could have been taken in the pipette the further dissolution is minimal and doesn't really influence the result." is not backed by evidence and does not follow pharmacopoeial recommendations to filter samples immediately (see USP Chapter<711>).

e) (Point g of the original NOC) There were no training records available, at all, for the analyst performing these tests, who had been working for the laboratory for approximately one year prior to the inspection.

In your response, you stated:

> *"We reconfirm that training was imparted to the person concerned and the record was available. Unfortunately, this could not be resolved in the course of inspection. The copy of the training record of Umesh (HPLC Analyst) is attached for your reference. Refer Annexure - 4.*
> *Doing the test under the eyes of an inspector is not normal for the laboratory personnel, so the risk of mistakes is much greater on such a moment."*

The above-mentioned training records, only include a training record of 30 minutes on "operation and calibration of dissolution" and a training evaluation questionnaire. This does not constitute adequate evidence of the Analyst's ability to actually perform the test. Furthermore, the test was performed twice in front of inspectors.

.../...

f) (Point h of the original NOC) Internal calibration reports for paddle speed were available but the declared measurements did not appear to have been done for rpm. The optical tachometer could not measure accurate speed without the reflective marker stickers which were purchased and added only after the inspector request. The measured value of rotation speed and temperature for the six testing vessels were outside of acceptable limits and showed a large difference with those recorded in the recent calibration report.

In your response, you stated:

> *"This happened due to low battery of tachometer. We will ensure that spare reflective markers are readily available every time during calibration".*

This response is inadequate because it does not show good understanding of the root cause of the issue. There was no adequate explanation provided on how measurements declared in previous internal calibration reports were taken and since your staff were unaware that reflective stickers were necessary to perform the test, we are still concerned that calibration data could have been falsified and that an out-of-calibration instrument had been used to test your products. Furthermore, out of range rotation speed went undetected until this inspection and the plausibility of your explanation that the rotation speed was out of range due to the "tachometer battery being low" is doubtful.

g) (Point i of the original NOC) There were issues with the temperature controls of the heating device in the dissolution bath – the media could not reach the minimum of 36.5 °C in the vessel. Furthermore, the difference between the temperatures of the different vessels exceeded the limits of 0.4 °C.

In your response, you stated that new dissolution apparatus will eliminate any concern. However, this does not address the issue of this problem having gone unnoticed until this inspection or how and why it had occurred in the first place.

h) (Point h of the original NOC) Preventive maintenance only consisted of calibration steps, there was no maintenance procedure in place. The instrument logbook did not include any information on preventive maintenance, or instrument malfunction.

The above deficiencies raise questions on the reliability of the dissolution results obtained for batches released into the market and of the data submitted in the dossiers up to date. Safety, quality and efficacy of products can therefore not be guaranteed. Your rationale that several released batches were tested by SGS laboratories and were not out of specifications does not provide sufficient assurance that your quality control unit is able to carry out its responsibilities or that all batches released onto the market meet specification limits.

2. *The company failed to ensure the integrity of data:*

a) Several analyses were seen (e.g., HPLC QC IN 067) without records of the analysis being made in the instrument logbook and without being retrievable in official analytical reports. This practice was not covered by any SOP in the laboratory. Batch numbers were not electronically recorded. Samples were injected prior to the official analyses. Company staff confirmed that sample trial injections were performed. For instance:

> - (Second point of the original NOC - shortened) On instrument HPLC QC/IN/067, hundreds of trial injections called "TRIAL000001.D" in sequence, were seen in folder "c:/CHEM32/1/DATA". These were subdivided by date of analysis. Other similar folders existed. Within these folders, the example of 024-0401.D, 4FDC, file path

.../...

C:/CHEM32/DATA/28062013 2013-06-28 04-25-03/, dated 28 June 2013, 13: 26:17, was randomly selected. It showed six injections, labelled as "Dissolution-1 sample,..etc".

-(Third point of the original NOC – shortened) Another trial injection performed on the same date for the 4FDC, this time named C:/CHEM32/DATA/28062013 2013-06-28 04-25-14/ Dissolution - 1, dated 28 June 2013, 4:26:42, with peak areas of 1523.2, 5897.1, and 3955.1 for rifampicin was also obtained. The test result corresponded to approximately 80.0% - it did not match results obtained for other tablets within the batch or the path file name.

- (Fourth point of the original NOC) Another injection named 280614 2014-06-28 01-11-19 could not be opened as the files appeared to have been deleted (file folder empty except for file name 024-0401.D. which came up as "invalid file path name").

b) Data was found to be deleted for several runs. In the example of instrument QC/IN/053:

- A run named "050514 2014-05/05 22-11-51" saved on C:/CHEMSTATION/1/DATA, for rifampicin 60 mg/isoniazid 60 mg tablets. The date appeared to be erroneous, with a reading of 01/01/0001 at 12:00 am;

- A run named "131214 2014-12-13 13-56-44", where three injections were performed for vials 4, 5, 6 as samples, with data file names of 004-0101.D, 005-0201.D and 006-0301.D, starting from 13 December 2014 1:58:01 pm; and

- The recycler of c: / on HPLC QC/IN/054 recycler had a folder entitled "S-1-5-21-1220945662-776561741-1801674531-1003", with a filename of "002-0101.D", which could not be opened as it had been deleted.

Your responses to points a) and b) stated that two new HPLCs and one new GC were ordered, along with server based software and that the systems will be connected to a centralized server. Your response also stated that once these systems would be implemented, "all the concerns regarding the integrity of data will be resolved completely". This response is inadequate because new equipment and usage of a server, on its own, is not deemed sufficient to ensure the absence of data integrity issues and to prevent the manipulation of analytical data.

Also, your response to point a) stated that trial injections of diluents and standard were performed and that batch numbers were not electronically recorded because these were standard injections. You also stated that your SOP was revised to include the recording of trial injections and printouts. You did not provide any evidence in support of your claims that the injections performed were standards and in any case, in some of the specific examples mentioned in this letter, the data seen showed otherwise, since they were named "sample" and had sample sets and concentrations comparable to those used for the testing of samples. Also, with regards to electronic chromatographic data that could not be retrieved because it had been deleted, the inspector requested several times for the data to be restored during the inspection but this could not be done. Your statement that the data was not deleted is not supported by any evidence and you did not provide a valid or clear explanation why the data was no longer available on the systems under review during the inspection, or why the back-ups could not be restored during the inspection.

c) (Point e of the original NOC) Instrument audit trails were not available except for login and logouts/password entry. There were no audit trails enabling to see deletion of chromatographic data or filename changes.

.../...

In your response, you stated that two instruments had audit trails since 2008 and that three other instruments had audit trails since March 2015. During the inspection, the inspectors repeatedly requested to see the audit trails on HPLC QC/IN/054 and HPLC QC/IN/067 which were operated using Chemstore software, and the only audit trails which were shown only captured login and logout password entry. Your explanation that "the audit trails can only be seen by administrator" is not a valid explanation given the fact that the inspector also requested for the administrator to show audit trails to inspectors with a similar observation. Furthermore, your response is inadequate in that it does not provide any supporting evidence on what exactly your audit trails were configured to record or for how long these settings had been in place and whether these were different from those shown during the inspection.

d) (Point f of the original NOC) On Day four, an analyst was seen in process of taking tablet weight data from a calculation spreadsheet in Excel® and writing the values down in his analytical test sheet as if these were the raw weighting values. (This was for process validation batch SL-172 of the 3FDC, manufactured in May 2015). The original weighing measurement values were not available. No explanation was provided to this and laboratory supervisors, when asked about this, claimed that the analytical test sheet contained the original measurement values, which was untrue.

In your response, you stated:

> *"Raw data for the test performed were recorded in another notebook, as before this practise of issuance and recording of data in TDS was not practiced for validation samples. The concerned analyst had compiled all the raw data on to an excel sheet on a PC available in the laboratory. During the process, the supervisor advised the concerned analyst to maintain the TDS for the same for better traceability and review of data in future. The concerned analyst was transcribing the values on the excel sheet in the TDS. The instructions from the supervisor were not as per SOP however he tried to maintain Good Laboratory Practices. In order to address this discrepancy in communication the SOP "HPLC Analytical Testing and documentation QC/161. (Refer Annexure 6 attached herewith) is being revised to incorporate the requirement to maintain all the raw data in the TDS issued for the same. Training on this revision in SOP has been performed."*

This response is inadequate because it does not admit to the fact that the original raw data was unavailable. Raw data/logbooks were requested at least twice by the inspector to both the analyst and to his supervisor for this data but were claimed not to be available. Furthermore, this response does not address why the current quality management system had allowed such practices to take place.

e) (Point h of the original NOC) The company was unable to demonstrate their ability to readily restore data that was archived or backed-up for HPLC equipment.

In your response, you stated that the data was kept on an external disk for all instruments and that from now on, a dedicated server will be installed in addition to off-site back up. Your response is inadequate in that it did not explain why missing/deleted data and historical data could not be restored during the inspection despite the request having been made twice by inspectors.

3. *The company failed to adequately conduct stability tests in line with stability protocols and commitments:*

False and misleading statements were made in stability reports and in the Product Quality Reviews (PQR) for 2014 for the 3FDC product. For example, the stability protocol for ongoing stability, for batch SL58, 28 tablets in blister pack of aluminium/PVDC in laminated carton, at 30 °C/75%RH, batch size of 1,010,000 tablets had already been signed off as "approved" and stated that all test

results, including the related substances test, were within the specification limits. Inspectors found that the test for related substances had actually not yet been done for any of the time-points for the 30 °C/75%RH and 25 °C/60%RH condition – the company declared that this test was done only at the final time-point, which is not conforming to the protocol or stability commitments/requirements. According to the protocol, the product should have been tested at 3, 6, 9, 12 and 18 month time-points. The signed and approved stability report was dated January 2015.

In your response, you submitted a stability testing report, dated 19 July 2015, for the 30 °C/75%RH condition, showing a protocol for related substances testing of initial, 6 months, 12 months, 24 and 36 months. The report contains related substances test results for initial, 6 and 24 months. Your response is inadequate because you did not explain why the stability report for the 18 month 30 °C/75%RH time-point that had been reviewed by the inspector, during the inspection, had stated that the related substances test was within limits. Also, the document submitted shows that you missed the 12 month time-point. Furthermore, you did not explain the basis of your reduced testing protocol for related substances (i.e., not testing at all time-points). Your explanation that stability studies have been submitted to WHO prequalification and that stability data was reviewed during all earlier audits by WHO, does not address this issue, since inspections are sampling exercises and assessments rely on the accuracy and completeness of all declarations being made.

4. *The company failed to maintain adequate records of equipment usage and failed to ensure data integrity in production:*

The logbooks for usage and cleaning of production equipment for 2015 (e.g. Fluid Bed Dryer (FBD) dryer logbook, sifter logbooks) were not legitimate and original records. For example, although the Vibrosifter Matrix 049 Logbook 78, indicated that "Employee R." had performed operations from 9:00 am to 19:20 on 14 May 2015 and "Employee M", had performed operations from 23:40 on 14 May 2015 to 3:40 on 15 May 2015, they did not write their own records, because all of their logbook entries were of the same handwriting and the person writing these entries, could not have been present this entire time, since it spanned periods of 24 hours which did not conform to regular shifts. Logbooks often showed several weeks of activities recorded by the same person for entries taking place 24 hours/7 days of the week.

In your response, you stated "the entries in the log book were made from the raw data appearing from the Batch Manufacturing Record, by one of the production officer, which was later counter signed by another officer". This constitutes falsification and backdating of records that were supposed to be taken contemporaneously. Such practices raise serious concerns regarding the integrity, reliability and accuracy of the data generated and available at your facility.

5. *(Previously Point 6 of the original NOC – reclassified from major to critical due to inadequate response) The company failed to provide adequate controls of contamination and cross-contamination of the product:*

a) The granulation equipment cleaning room floor was uneven and crumbling next to the drain. Black mold was found in significant amounts inside the drain, which contained stagnant water.
b) Granulation equipment had a significant amount of chips and scratches and rust spots.
c) The rubber seals in the granulation equipment and fluid bed dryer had many pieces missing. A small piece of rubber was seen on the sifting filter of the 200 kg capacity fluid bed granulator in the same room.
d) Peeling wall seals were seen, which could have released particles in the area.
e) The fluid bed dry filter had small rips in it.

.../...

Your response is inadequate because, although you claim to have corrected some of the specific areas pointed out to you as being sources of contamination/cross-contamination, you did not describe corrective actions taken for other parts of your facilities or explain why your current quality management system had allowed such issues to occur. As stated in the letter dated 8 July 2015 that was sent to you along with the inspection report, an inspection of this nature is a sampling exercise. The response should have incorporated root cause analysis and analysis regarding other related areas in your production unit, correction and corrective action (to prevent recurrence) and the steps that have or will be taken for the demonstration of effectiveness of the actions taken. The risk of products being contaminated with material from the seals, should also have been assessed. You also denied the presence of the black mold, claiming that it was in fact stains, based on microbiological test results, without providing other supporting information or specific identification of the composition of these designated black stains or of their origin. Moreover, you did not state how you would prevent microbiological growth in the area located directly underneath the grille in the drain due to stagnant water. Overall, this response does not provide assurance that such problems will not be allowed to occur again in the future.

The major observations that are of particular concern, are:

6. *(Previously Point 5 of the original NOC – reclassified from critical to major due to a partially acceptable response) The company may have falsified analytical test data:*

The consumption of disodium hydrogen phosphate anhydrous was not in line with the number of tests claimed to have been performed. This reagent was used to prepare mobile phase in most of the tests related to the 4FDC, 3FDC and 2FDC. From the test data sheets and the testing monograph used by the company, the basic consumption of Na_2HPO_4 was:

-for release testing of each batch of the 4FDC: between 29.4 and 30.8 g (8.4-9.8 g for dissolution + HPLC, 1.4 g for assay, 16.8 g for content uniformity, 2.8 g for assay and content uniformity of ethambutol).

-for release testing of each batch of the 3FDC: between 9.8 and 11.2 g (8.4-9.8 g for dissolution + HPLC, 1.4 g for assay).

-for release testing of each batch of the 2FDC: between 9.8 and 11.2 g (8.4-9.8 g for dissolution + HPLC, 1.4 g for assay).

The most recent bottle of Na_2HPO_4 (500 g) was received on 20 December 2014 and was opened on 6 May 2015. Until the last day of inspection there was around 200 g of Na_2HPO_4 remaining in the bottle, while 145 individual weightings were counted through the balance usage logbook and 63 dissolution tests were performed from the date of opening of this bottle. The consumption should have been 529 g, at minimum (63 batches of dissolution multiplied by 8.4 g/batch), which did not match the quantity of Na_2HPO_4 remaining in that bottle.

Furthermore, during the inspection, the company provided records only for the following bottles of Na_2HPO_4 from February 2014.

Receiving date	*Quantity*	*State of usage*
6 February 2014	4 x 500 g	No bottles in stock (all consumed)
2 July 2014	1 x 500 g	No bottles in stock (all consumed)
5 August 2014	6 x 500 g	No bottles in stock (all consumed)
10 September 2014	4 x 500 g	Not consumed – bottles not opened
23 December 2014	4 x 500 g	1 bottle in stock (not consumed, bottle not opened) and half bottle was under use
4 March 2015	5 x 500 g	5 bottles in stock (Not consumed – bottles not opened)
8 April 2015	2 x 500 g	2 bottles in stock (Not consumed – bottles not opened)

.../...

After the inspection, further to an inspector query, the company provided invoices for 12 supplementary bottles, without a clear account of when the bottles had been opened and finished or where the remaining bottles were currently stored. It is not clear why the invoices could not be presented during the inspection.

Your response is inadequate in that it does not provide an acceptable explanation for the discrepancies between what should have been consumed, and what was actually consumed. Your proposal to record stock consumption of all the required reagents, is acceptable, but does not address the concern of misrepresentation in dissolution and other test data.

7. *The company failed to maintain adequate standards of housekeeping and hygiene:*

a) An area containing large amounts of food trash and manufacturing waste was found in an outdoor area – doors adjacent to this, leading to the workers change rooms, were left open which could have allowed the entry of pests and contamination. The floor plans had shown an airlock in this area.
b) The primary change room area for workers and corridors on the level ground floor had water and dirt on the floors. There were no instructions on removal of street clothing to change into company clothing. Food/dishes were being cleaned in this area.
c) Workers entering the stairs and airlocks/secondary change rooms leading to production, could have carried contamination from the ground floor to these areas. Water was visible on the floor of a secondary change room from their shoes.

With regards to point a), Your response is inadequate in that it did not explain why the design and usage of the area was different from that of the floor plan, why the doors were open to the outside and to the scrap area and it did not propose any corrections other than putting the scrap area under lock and key.

With regards to points b) and c), your response is inadequate in that you did not take true corrective measures to ensure resolution of this issue, which could be due to a lack of adequate segregation of activities, insufficient space relative to the number of contract workers and staff in the area, inadequate design of the area and an insufficient frequency of cleaning. The training records provided entitled "Primary gowning procedure" does not address the issue in that it only states "briefly explained gowning procedure to be followed after entering the factory premises for contract workmen" and the "format for daily checks of hygienic & sanitary conditions within factory premises" is only meant for performing checks once per day, which may not be sufficient on its own to resolve these issues.

8. *The company failed to maintain adequate and true records for in-process controls in production:*

a) The tablet hardness tester located in the room leading to compression cubicle 3, had a calibration tag but could not be adequately calibrated since it was not set to 0, its tip was rusty and did not appear to be in a good shape as some parts were loose. Hardness test results obtained with this tester could therefore have been unreliable.
b) The in-process parameters of the Sejong compression machine were displaying an alarm due to out of range parameters for thickness, yet this had not been recorded in the Batch Manufacturing Records (BMRs) and no action had been taken.
c) The tablet inspection step was not recorded in the BMRs. Many broken or stained tablets were seen during the inspection process. As witnessed by the inspectors, several broken tablets of the 4FDC were missed by the inspection step and were seen to reach the blistering stage.
d) The average weight and group weight of 20 tablets were not taken within appropriate time limits during the compression stage that was witnessed by inspectors in Compression cubicle 3 and were approximately 20 minutes late.
e) Similarly, the controls on secondary packaging and blisters were not performed within appropriate time limits.

.../...

Your response to point a) is inadequate in that it does not provide an assessment of the impact that unreliable hardness test results could have had on your ability to detect compression problems or on the quality of the product that you have released to the market. Also, it does not address why your quality management system allowed unacceptable and un-calibrated equipment to be used routinely.

Your response to point b) is inadequate because you did not provide clear evidence that this was simply an issue due to the fact that the touch screen was under setup mode. The photo provided of the Sejong machine screen, dated from 20 July 2015 is not considered relevant or sufficient evidence in support of your claims.

Your response to point c) is inadequate because you did not provide evidence that defects were indeed within normal ranges on a consistent basis.

Your response to points d) and e), claiming that chemists were unable to perform the activity because of the inspector's presence, is unacceptable. Inspectors did not prevent operation staff from performing their activities and no deviation or incident record was filed by your company. Also, you did not propose any concrete measure to avoid such errors being made in the future.

9. *The company failed to package products under adequate conditions on blister packaging lines:*

a) A large amount of rusty equipment parts and unclean surfaces contaminated with grease and oil, possibly releasing metal particles into the blisters and contaminating tablets, were seen.
b) The manufacturing date stamp (done by embossing on the blisters), was held by tape.
c) Replacement equipment parts were also rusty.
d) There was no second check of the number of blisters in each box. Boxes or carton packers were not weighed to confirm that they contained the right amount of blisters.

Your response is inadequate –You stated that the equipment was cleaned and painted and provided the picture of one of the blistering lines as evidence, but did not perform any assessment of the adequacy of painting as a corrective measure for various parts of the equipment, especially the heavily corroded parts that are frequently coming in contact with the product or that are being subjected to heat or friction. You did not mention whether or not you had addressed the need for equipment requalification further to this repainting and you did not provide any service reports, describing the work done on the equipment. It is not clear from which blistering line the picture was taken, as you did not specifically identify the piece of equipment and there are six lines located in your primary packaging unit.

10. *The company failed to ensure cleanliness of the air supply to manufacturing areas where the product may have been exposed:*

The air supply in the granulation room was not coming through a duct. The broken edge of a cement block and wire was seen from the HVAC air inlet grille in the granulation room. There was no terminal HEPA filter. Particles from the cement or area between the floors could have been released into the granulation equipment when opened to unload or upload granulation mixes.

Your response is inadequate – your statement that this supply air point was validated showing no problem of particle counts even though some concrete walls were exposed, is unacceptable and incompatible with good manufacturing practices. Your corrective action of covering the concrete wall with GI sheet, does not provide sufficient information on how the entry of unfiltered air in the production area will be prevented. Furthermore, you did not provide any details or evaluation on whether similar maintenance and design issues were occurring in the other air supply points in your facility.

.../...

The above examples raise serious concerns regarding the integrity, reliability and accuracy of the data generated and available at your manufacturing site and on your ability to prevent contamination and cross-contamination of your products. In your response to this letter, you are requested to provide an independent and comprehensive evaluation of the extent of the deletion of records, a risk assessment regarding the potential impact on the quality of products, and a comprehensive corrective and preventive action plan. Your submission should include a summary report of your evaluation of the data and records related to the manufacture (including testing, holding, etc.) of all drug products produced at your site over the last year (12 months). This evaluation should include a detailed investigation of other instances in which your operations and quality units failed to ensure proper testing of materials, or appropriate review of laboratory results and production data. All other instances of missing, inaccurate or unreliable tests results that are found, should be described in your response to this letter. Your investigation should assess the impact of all these incidents on the quality of the drug products manufactured and released into distribution, and explain the systemic actions that will be instituted to prevent these fundamental breaches of data integrity and management oversight in the future.

Accordingly, you should include a detailed description of your plans to implement a robust quality system in your response to this letter. This remediation plan should describe the broader steps you will be taking to ensure direct corporate oversight over the quality and operations functions of this facility. This system should ensure sustainable compliance with WHO GMP, including the basic capability to prevent data manipulation and destruction of electronic records.

It is highly recommended that you hire a third party auditor, with experience in detecting data integrity problems, to assist you with this evaluation and to assist with your overall compliance with WHO GMP. It is your responsibility to ensure that data generated during operations is accurate and that the results reported are a true representation of the quality of your drug products.

WHO will also withhold prequalification of all new products manufactured at this site until these critical and major observations have been satisfactorily addressed and WHO has verified and confirmed the acceptability of the corrective actions. In addition, if these critical and major observations are not corrected within a reasonable timeframe, WHO will suspend the product listed as prequalified from your manufacturing site, and recommend suspension of procurement of all prequalified products 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:

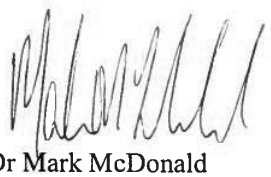
"3.(4) to ensure that the prequalification review process and the results of inspection and assessment reports of the listed products, aside from proprietary and confidential information, are made publicly available;"

In accordance with the above resolution and the NOC procedure, you were given the opportunity to provide corrective actions for the NOC. Since the corrective actions submitted on 23 July 2015 and on 3 August 2015, in response to the initial NOC letter that was sent to you, are unacceptable, we may proceed with immediate publication of this revised NOC. Please note that the NOC will remain active on the WHO-PQT website until satisfactory corrective actions have been submitted and accepted by WHO.

.../...

Should you disagree with the reasons for issuing this NOC, you are advised to email the WHO-PQT Coordinator with details, at 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 Head, Regulation of Medicines and other Health Technologies 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