World Health Organization

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

Your reference:

Mr Avinash Waghale
General Manager – Vaccines and Biologicals
Cadila Healthcare Limited
Sarkhej Bavla N. H. No. 8A, Moraiya
Tal. Sanand, Dist. Ahmedabad
382 210, Gujarat
Inde

29 January 2016

Dear Mr Waghale,

Prequalification Team – Inspection Services
Notice of Concern

Site of Manufacture: Sarkhej Bavla N. H. No. 8A, Moraiya, Tal. Sanand, Dist. Ahmedabad 382 210, Gujarat, India

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). Hence, this notice is issued in accordance with this procedure.

An inspection of your pharmaceutical product manufacturing facility at Sarkhej Bavla N. H. No. 8A, Moraiya, Tal. Sanand, Dist. Ahmedabad 382 210, Gujarat, India, was conducted by inspectors from WHO-PQT from 26 to 30 October 2015, pertaining to VaxiRab N and Lyssavac N vaccines. This inspection revealed several major deviations from the WHO GMP 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. The last day of the inspection, a copy of the raised deficiencies was left to your attention on 30 October 2015.

Following the inspection, a copy of the inspection report was sent to you by email on 14 December 2015. Also, a NOC letter was sent to you on 23 November 2015. Due to the seriousness of the deficiencies raised, you were requested to respond to the observations listed in the NOC and in the inspection report within 30 days from the date of the letter. You replied to the observations listed in the inspection report, as well as to those listed in this NOC on 22 December 2015.

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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 the information submitted up to date:

1. The company failed to record and report reliable and accurate data for the environmental monitoring results [WHO TRS 986 Annex 2, sections 1.1, 1.5, 2.1, 15.1, 15.6, 17.1, 17.3 (f)].

   The following critical Data Integrity issues in form of apparent fraudulent data were witnessed during the inspection:

- False results have been recorded on the Quality Control (QC) records and reports. It was witnessed that the plates recorded and reported as negative by Cadila QC personnel were in fact positive for contaminations as mentioned below.
- Contaminations (colony forming unit (cfu) counts) in grade A were recorded and reported as nil but in fact were positive. Contaminations of grade B were recorded and reported as nil or as within the specification of established alert limit but in fact they were positive and above the specified limit. Contaminations (cfu counts) for operators gown in grade B were reported as nil but in fact they were positive.
- The settle plate count on the exposure date of 20 October 2015 was observed on 25 October 2015 and reported as within the specifications. However, the plate n° V23 LAF-Cap sealing of grade A (in Vaccine-R filling area) falsely reported as having nil count whereas in fact it contained 16 cfu. The plate VA9 Center of room (grade B) was falsely reported as containing 3 cfu count but in fact contained 11 cfu. Personnel monitoring glove in grade B was also falsely reported as nil but was positive (1 cfu). The plate VA12 LAF in filtration room of grade A was falsely reported as nil but was positive (1 cfu). The plate V19 in the cooling zone was falsely reported as nil but was positive (1 cfu).

The company has initiated a comprehensive investigation on the falsification of data and on the excursion in environment monitoring count.

The company has provided details evidencing the cases of falsely reported environmental monitoring results. A summary of the information provided by the company is presented below.

From the falsification data standpoint the company concluded that:

- *The microbiologist was casual in his approach towards work.*
- *Lack of review mechanism in the laboratory.*
- *Lack of supervision by the laboratory head.*
- *No Quality Assurance (QA) oversight in the laboratory.*

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The corrective and preventive actions (CAPA) have been provided by the company as follows:

Action / Activity	***Target date***
Recall of all the batches of Rabies Vaccine manufactured from April 2015 until date was initiated.	*Completed*
Manufacturing of Rabies Vaccine has been suspended.	*Completed*
Further to evaluate if data reliability is a systemic issue, a protocol based evaluation will be done for the documents generated since April 2015. Refer to Exhibit VI "Protocol for Authentication of data for its traceability, accuracy and reliability". The rationale for duration is based on the last two successful media fill in October 2015 and April 2015 and date of initiation of Environmental Monitoring (EM) by the said microbiologist. The review includes: *a. batch manufacturing records and its traceability* *b. analytical records and its raw data for its traceability.* *c. all the documents related to quality assurance functions i.e. change controls, deviation controls, incidents, market complaints, Validation and qualification, self-inspection, failures.* *d. media run and area requalification* *e. training record of personnel.* *Note: In case of any concern on data accuracy and correctness, which may affect the safety, identity, strength, purity and quality of the product, the review will be extended to two years (shelf-life of product).*	*March 2016*
Counselling on importance of Data Integrity have been provided to all the employees of vaccine department.	*Completed*
A corporate policy on Data Integrity will be prepared in line with: *a. WHOTRS 986* *b. MHRA GMP Data Integrity Definitions and Guidance for Industry Revision 1.1, March 2015* *c. "Guidance on good data and record management practices" Working document QAS/15.624 September 2015.*	*January 2016*
The microbiologist has been taken out from all QC activities.	*Completed*
Action has been taken against the reviewer and supervisor of the microbiology laboratory.	*Completed*
Pledge for ethical quality conduct is signed by all the employees including senior management.	*Completed*
Doer checker concept (observation by two persons) has been implemented for data related to environment monitoring in quality control laboratory. The corresponding procedure "Environment monitoring of clean rooms by settle plate, Air sampling, Surface monitoring and personnel monitoring for viable count-Vaccine-R (Pharma block)" has now been revised and implemented. The procedure has been revised for documented evidence to prove that the environment monitoring plates are free of any contamination and intact before use. *The procedure titled "Environment monitoring of clean rooms by settle plate, air sampling surface monitoring and personnel monitoring for viable count-Vaccine R (Pharma Block)" and the procedure titled "Preparation, Receipt, Testing and use of SCD agar plates".*	*implemented*
Implementation of QA in QC Microbiology	*January 2016*
Random review of daily environment monitoring plate by QA. *The corresponding Standard Operation Procedures (SOP) SOP/QR/251 titled "Procedure for observation of Environment monitoring plates after incubation" has been prepared and implemented.*	*Implemented*
Reporting of Vaccine QA head and Vaccine QC head to the Moraiya site Quality head.	*Implemented*

Review of documents of all the activities wherein the said microbiologist was involved (i.e. temperature / humidity monitoring for QC laboratory and differential pressure of Laminar air flow (LAF) in QC, calibration of pH meter).	*March 2016*
An independent third party audit shall be conducted, to assess the state of compliance and adherence to current GMP requirements.	*Before re-submission of Product Summary File to WHO.*

Additional action for enhancement for reliability and accuracy of the data:

Action / Activity	***Target date***
Installation of colony Counter (electronic plate reader) for the reading of environment monitoring plates. Refer to Exhibit XI "Salient features of Colony Counter".	*January 2016*
Implementation of LONZA MODA software to enhance the compliance.	*December 2016*
Laboratory Information Management System (LIMS).	*March 2016*
Electronic document management of Quality Management System (QMS) (By TrackWise).	*July 2016*
Manpower in quality assurance, quality control and manufacturing will be augmented to ensure the commitments to compliance.	*April 2016*
Further to enhance the quality culture following efforts have been initiated/planned. External Subject Matter Expert, McKinsey & Co. engaged for support in driving "Quality Culture" and "Risk Management from Design to Delivery". *The quality culture includes the following:* *I. People ownership:* • *speak up for quality* • *empowerment* • *knowledge management* *II. Continuous improvements:* • *continual improvement philosophy* • *metrics driven* *III. Process Excellence:* • *manufacturing process excellence* • *QMS process excellence.*	*December 2016*

<u>From the excursion in environment monitoring count standpoint the company concluded that:</u>

- *The HEPA filters in the filling and lyophilization area were found failing in filter integrity test.*
- *The procedure "Environment monitoring of clean rooms by settle plate, Air sampling, Surface monitoring and personnel monitoring for viable count-Vaccine-R (Pharma block)" was found to be deficient as the monitoring of plate doesn't include the doer checker concept.*

Action / Activity	***Target date***
Procedure for environment monitoring "Environment monitoring of clean rooms by settle plate, Air sampling, Surface monitoring and personnel monitoring for viable count-Vaccine-R (Pharma block)" and the procedure titled "Preparation, Receipt, Testing and use of SCD agar plates" are revised to incorporate the following: • *Documented evidence to prove that the environment monitoring plates are free of any contamination and intact before use.* • *Independent review of environment monitoring plates by the second person.*	*Completed*

Air sampling in Grade A by using sterilized lid instead of sanitization.	*March 2016*
An independent third party audit shall be conducted, to assess the state of compliance and adherence to current GMP requirements.	*Before submission of Product Summary File to WHO.*

Additional actions for enhancement of sterility assurance to be taken by the company have been provided as follows:

Action/Activity	***Target date***
Procedure for cleaning and sanitization has been revised for better sterility assurance. Procedure titled "Area Cleaning and disinfection procedure of Pharma Block".	*Implemented*
Three gowning procedure implemented in aseptic area instead of two gowns.	*Implemented*
Online NVPC location in Grade B.	*March 2016*
Online viable monitoring system in grade A.	*March 2016*
Training to aseptic area operators by using: • *video of smoke study of aseptic area* • *video of gowning practices* • *video of good aseptic practices* • *do's and don'ts in aseptic area.*	*January 2016*
Sterile hand gloves checking for its intactness during each exit from aseptic area.	*Implemented*
Installation of "No touch system" in door interlocking in aseptic area.	*June 2016*
Semi-automatic loading system of vials in lyophilizer.	*June 2016*
0-RABS installation and print out of 0-RABS for every intervention.	*October 2016*
Risk based approach for identification of EM location and frequency.	*January 2016*
For sterile hand gloves - Sterility test, pin hole test, pack intactness test to be carried out for better control in aseptic area from six monthly carried out for better control in aseptic area.	*January 2016*
Frequency of qualification of HEPA filters to be changed months for the next one year.	*January 2016*
In addition to requalification of area, Performance Qualification of Auto Clave, dry heat sterilizer/tunnel and lyophilizer to be performed before due date.	*March 2016*

2. The company failed to implement an adequate quality assurance system as evidenced by the following (WHO TRS 986 Annex 2, sections 1.1, 1.5-6, 1.10, 2.1, 8.1-6, 9, 12.1-10).

- Sterility failures occurred and were not reported, investigated/ documented nor even reported to the inspectors:
  a. Five batches of virus harvests were rejected due to contamination. However, there were no report initiated.
  b. One batch fail during filling/break down of lyophilisation process (batch number RO108 dated 14 May 2015). No action or suitable report was provided for this incident.
- It is a common practice by the company to investigate the sterility failure only in the case if more than one jar fails for sterility per batch of first or second harvest. This was evidenced by the following:
  - Harvesting and sterility SOP/CR/015 describes the steps to be followed for the collection of rabies virus harvest and performing the sterility of the harvest. Under section 7.2.3 Sterility failure limit of first and second harvest it is stated that:
    i. Limit of failure of first harvest is one jar of 20 L per batch of first harvest.
    ii. Limit of failure of second harvest is one jar of 20 L per batch of second harvest.

This is not acceptable and that should be adequately addressed. Failures should be reported, deviations should be initiated, and investigations into root causes analysis must be implemented. Batch rejection should be considered unless otherwise duly justified and documented.

The CAPA implemented by the company included the revision of the procedure titled "Harvesting and Sterility" in order to carry out investigation in case of any sterility failure.

Further taking this as reference a protocol based review for all critical deviations and incident of past one year will be done for its adequacy. In this case, if any reinvestigation impacts the product safety, identity, efficacy, strength, purity and quality, a suitable action shall be initiated. The target date of completion by the company is April 2016.

3. The Annual Product Review (APR) management was not considered acceptable and gave rise to a major deficiency that should be addressed (WHO TRS 986 Annex2, section 1.10).

- The APR for the manufacturing process up to formulated bulk was never considered.
- The APR for diluent was not considered.
- In addition, the APR year 2014 for VaxiRab NTM and ZOONOVACTM was considered deficient in the following:
  a. The APR covered batches manufactured in 2014 including only final formulated bulk steps and finishing. There is no trend analysis for results that were presented in non-validated Excel spreadsheets. Some deviations were considered as incidents only and therefore there was no appropriate investigation or CAPAs have been generated.
  b. Quality agreements with third parties are not considered for reviews in the APR.
  c. The reviews of CAPA from previous APR are not taken into account.

The CAPAs proposed by the company included:

- *The revision of the procedure titled "Annual Product Quality Review" to include the following:*
  - *Annual Product Quality Review (APQR) for all manufacturing stage including bulk manufacturing*

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- *APQR for diluents used in the manufacturing of product*
- *review of CAPA from previous APQR*
- *status of quality agreement with any external party.*

- *The trend data of APQR of year 2014 will be executed using Minitab and compared with the trend of 2014 executed using Excel spreadsheet.*
- *The procedure titled "Incident Reporting" has been revised to include the investigation, root cause identification, impact assessment and risk assessment. Refer to Exhibit XVI SOP/BQA/024 title "Incident Reporting".*
- *Based on the outcome of review of trend data using Minitab the impact assessment will be determined, and if there is an impact on product safety, identity, strength, purity and quality, a suitable action will be taken.*

The target date of completion by the company is April 2016.

4. There was no management review meeting in place (WHO TRS 986 Annex 2, sections 1.6).

The CAPAs proposed by the company included the following:

- *Corporate policy on management review meeting has now been extended to the facility which include: monthly meetings at plant level and quarterly meetings at management level as per procedure titled "Management Responsibility". The highlights of the policy are as follows:*

  - *The monthly review shall include the following:*
    - *site quality index*
    - *status on 24 X 7 compliance*
    - *product quality /stability /OOS /Analytical method related issues and action plan*
    - *investigation and repetitive cause for failure*
    - *compliance status /CAPA tracker status /open CAPA*
    - *area of concern with suggested action plan*
    - *new learning*
    - *technology transfer and process validation status*
    - *major changes*
    - *personnel training.*

  - *The quarterly review shall include the following:*
    - *systemic deficiency reported*
    - *review of process performance, product quality performance and compliance to quality systems*
    - *global CAPA management*
    - *necessary initiation of budget /automation /personnel approval*
    - *follow up action and evaluation of effectiveness of action.*

5. Change control handling was deficient in the following [WHO TRS 986 Annex 2, sections 1.5(n)].

- Change control are categorized as critical, major and minor according to the quality impact to the product. Effectiveness check was not considered in the change control procedure.
- No impact or risk assessment to the quality of the product has been considered during change control process. (CC15/VC/077: 3 sampling points for continuous particles monitoring were installed in the filling line without considering the assessment of the impact or risk to the product during the change control handling).

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The corrective action initiated by the company which is "Protocol based study" to reopen last two years of change control related to vaccine manufacturing to review for effectiveness check, impact and risk assessment.

In this case, if any impact on the product safety, identity, efficacy strength, purity and quality is determined, a suitable action shall be initiated.

The target date of completion by the company is April 2016. The preventive action implemented by the company includes the change control titled "Change Control", was revised in line with the corporate policy and now included impact and risk assessment as well as effectiveness check.

6. Deviation Management was considered weak in the following [WHO TRS 986 Annex 2, sections 1.5(s)].

   6.1 No deviations categorisation system is in place. A change control to revise the deviation procedure was initiated.

The CAPA considered for implementation by the company includes the revision of the procedure for handing of deviation which consist of categorizing of deviation as critical, major and minor based on the assessment as well as risk assessment for critical and major deviation.

The company stated that all deviations which were raised in the past two years will be reopened, categorized as per the revised SOP. Critical and major deviations will be reviewed with respect to adequate impact analysis and risk assessment. In this case, if any re-assessment impacts the product safety, identity, efficacy, strength, purity and quality, a suitable action shall be initiated.

   6.2 Deviation DV/15/009: VaxiRab CO 116, during lyophilisation process, step 17 extended beyond the set time of 30 minutes. The power supplier was interrupted. Due to this power failure, sequence n° 17 of secondary drying was extended by 21 minutes. The test results of the batch impacted were within the established specifications including moisture content and potency. The batch was released without documenting or justifying the impact or risk assessment to the quality of the product.

The CAPAs proposed by the company:

- *Impact and risk assessment will be carried out.*
- *Retraining to be imparted to all section in-charge and quality assurance team who are involved in impact analysis and risk assessment.*

Also, the company stated that all deviations which were raised in the past two years will be reopened, categorized as per the revised SOP. Critical and major deviations will be reviewed with respect to adequate impact analysis and risk assessment.

7. Vendor qualification (WHO TRS 986 Annex 2, sections 7.5-8).

- The audit frequency should be revised. There should be risk assessment based studies to qualify the frequency of vendor's audit.
- Contracted laboratory (Venky's India Ltd). The copy of Cadila's audit checklist is not a controlled document (no header of footer or company's logo). Furthermore, the audit checklist was filled by the contracted laboratory, not by Cadila inspector/s.

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The CAPA considered by the company: all the contract laboratory audits conducted for the testing related to vaccine manufacturing will be reassessed for its adherence to corporate guidance document. Based on reassessment outcome, a re-audit will be performed wherever necessary.

8. The manufacturing facility DS I and Vaccine R Buildings were considered deficient in the following (WHO TRS 986 Annex 2, sections 12.1-2, 12.4-5, 12.10, 12.25, 12.30, 13.1-2).

- No separation room between the shower rooms and change of clothing room immediately before the entry to corridor of grade C.
- There were no airlocks between virus infection and and virus harvesting area of grade B and walk-in incubation I of grade C. Materials and personnel move from aseptic area of grade B to area of grade C and vice versa without any measures regarding the risk of contamination.
- Cold storage rooms were located in grade B areas.
- Non-classified cold room for harvest storage opens directly with simple door to the aseptic concentration and purification room of grade B. Materials and personnel move from aseptic area of grade B to non-classified area and vice versa contributing to the contamination of the aseptic area.
- Incubation room 20-25 °C was non-classified and opens directly with simple door to the wide corridor of grade C.
- Environmental monitoring media of non-infected and infected areas are incubated in non-classified incubation rooms 20-25 °C and 30-35 °C located in the wide corridor of grade C. Materials and personnel move from aseptic area of grade B to area of grade C and vice versa without any measures regarding the risk of contamination.
- Environmental monitoring media of non-infected and infected areas are moved through the manufacturing areas of grade B (virus infection & virus harvesting) to the wide dirty corridor to dirty corridor to be autoclaved.
- Environmental monitoring media of non-infected area are moved through infected area to be incubated in the incubation rooms in the wide corridor.
- The cross flows from non-classified areas through aseptic and infectious areas are not adequate and contribute to potential risks to the contamination and cross contamination of the manufacturing areas and to the product.
- No risk assessment was available for risk identification of potential risks of contaminating manufacturing areas and the product, especially that the product VaxiRab N is processed without any sterilisation process.
- Pressure is manually recorded every two hours by operators. Pressure monitoring is performed by Magnehelic gauge and no form of alarm system (visual or audible) was in place for any out of range for differential pressure.

The company confirms that the process area starting from egg receipt to bulk preparation area was reviewed for the area classification with reference to WHO guidance document "Environment monitoring of clean room in vaccine manufacturing facilities November 2012". Furthermore, the company proposed the following corrective actions:

- *Clothing area immediately before the entry corridor will be separated by providing separate entry/ exit. As per new classification, corridor will be claimed as Grade D.*
- *As per new classification, viral infection and viral harvesting area will be grade C. The material and personal movement from aseptic area of grade B to the area of grade C will be addressed. However, a pressure differential shall be maintained between both grade C areas*
- *Cold rooms will be modified to open in grade D areas.*
- *Grade B area will be claimed as grade C area as per new classification. Cold rooms will be modified to open in grade D areas. The personal movement and the material movement shall be separated from grade C to non-classified cold rooms and vice versa to avoid the contamination of aseptic area.*

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- *Non-classified cold rooms and vice versa to avoid the contamination of aseptic area.*
- *Separate entry will be provided from outside to the incubation room 20-25 °C. Personnel and material entry will be separated.*
- *Separate entry will be provided from outside to the incubation room 20-25°C. Personnel and material entry will be separated. The corridor will be classified as grade D and personnel movement to the unclassified incubation rooms will be restricted from corridor.*
- *For the movement of environment monitoring media for infected as well as non-infected area will be designed separately. The movement through the manufacturing area of grade C (virus infection and virus harvesting) will be restricted. Separate autoclave will be installed for discard of the media. Non-infected area plates shall be taken out and incubated in QC*
- *Separate incubation areas for environment monitoring media of non-infected area and infected area will be provided. Media from non-infected area shall be incubated in QC laboratory.*
- *The layout of area will be revised to avoid any cross flow from non-classified area to aseptic and infectious area. Risk assessment will be initiated to mitigate any potential risk to the product and contamination of area.*

The company committed to the following:

- *modification of area to be completed by April 2016 and the requalification by June 2016.*
- *The risk assessment for the facility, product/process and environment monitoring location has been initiated and the company committed for completion by March 2016.*
- *Risk based approach will be adopted to identify the critical area and audiovisual alarms will be installed in these areas. Alarm system will be qualified before implementation. The target completion is May 2016.*

9. Environmental monitoring in Vaccine R Building (filling) and in DS I Building (aseptic upstream process) is considered deficient in the following (WHO TRS 961 Annex 6, sections 4.21, 4.7-10, 11.10-11).

- The locations of the sampling points are not risk based and not based on the qualification results. Alert limits are not based on historical data.
- Grade D is not considered for monitoring for both microbial and non-viable particles (NVP) in Vaccine R building.
- Grade D is monitored for microbiological but not for NVP in DS I facility.
- Smoke test in dynamic conditions has not been considered by the company in DS I facility.
- No system is in place for triggering alarms during the particle monitoring during aseptic filing and processes.
- According to the change control CC15/VC/077, three sampling points for continuous particle monitoring were installed covering LAF-empty vial loading, LAF-filling needle and LAF-half stoppering for continuous particle monitoring. However, only one portable counter (Met-one Vac-R/PE/378) is used to monitor particles for 11 minutes in LAF-bunging table, LAF-Usifroid lyophilizer, LAF-BOC Edward Lyophilizer and LAF-B/W BOC and Usifroid lyophilizer. Monitoring in these locations of grade A via portable counter device is considered a high risk operation to the product.
- The same and only one available portable counter (Met-one Vac-R/PE/378) is used for the particle monitoring in filling line and for particle monitoring for grade B, C and D. Two minutes for purging are allowed before the portable count (Met-one) is transported from area of grade B to the filling line of grade A. No disinfection is performed when the Met-one is moved from grade B to the filling area of grade A. 70% IPA disinfection is performed when the Met-one is moved from area of grade C to the aseptic room of grade B. There is no documented evidence of the effectiveness of these measures.

The CAPAs provided by the company addressed the above deficiencies.

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10. The media fill management was considered deficient in that (WHO TRS 961 Annex 6, sections 2.3, 4.23-25)

- No procedure was in place for media fill Simulation and media bulk simulation.
- Media fill test is considered for finished products filled in vials including the manufacturing of inactivation of raw virus harvest. However, the media simulation for aseptic processes for upstream processes up to the pooling and primary inactivation was never considered for initial validation neither for routine aseptic media simulation without any justification or documentation.

The CAPA considered by the company mentioned that a risk assessment will be performed on process and area. The same will also be extended to upstream processes. Critical processes, steps and control points will be identified. Based on the risk assessment, the procedure on media fill simulation and media bulk simulation run will be prepared to include evaluation of all those identified critical processes and controls. Also, the protocol for conducting media run will also be revised adding assessment of all those identified steps. Three media fill runs will be executed as per the revised protocol. The target date of completion is June 2016.

11. The stabilizer containing gelatine and Human Albumin Serum is 0.22 µm filter sterilised. The sterilisation filter is pre and post integrity tested. However, the sterilisation process by 0.22 µm filter was not validated (WHO TRS 961 Annex 6, sections 7.7).

The CAPAs proposed by the company stated that all the intermediate solutions wherever sterilization grade 0.22 micrometre filter are used, filter validation will be carried out for the following:

- *microbial log reduction*
- *any leachable*
- *adsorption*
- *throughput*
- *limit for filter integrity with product.*

The target date of completion is June 2016.

The company findings coincide with the inspectors observations and showed that the company was operating far from WHO GMP for at least the incriminated period of time where fraudulent environmental monitoring results were casually reported. The Cadila Health Limited QMS in place failed to assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The strong commitment from the senior management of the company and the effective implementation of the CAPAs could lead to the compliance with the WHO GMPs and accordingly new Product Summary File (PSF) submission and GMP on-site inspection will be considered by WHO-PQT.

On 29 October 2015, Cadila Healthcare Limited informed WHO-PQT about the suspension of the manufacturing of Lyssavac N – Purified Duck Embryo Rabies Vaccine as well as about the intention to withdraw the application for prequalification of VaxiRab N (Purified Chick Embryo Cell Culture) vaccine.

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On 30 October 2015, Cadila Healthcare Limited provided to the WHO Inspection Team a list containing product names and batches of vaccines and biologicals for which a voluntary recall action had been initiated by Cadila Healthcare Limited. The list contained 64 final bulks / final finished batches of non-prequalified VaxiRab N vaccine and Prequalified Lyssavac N vaccines ready for dispatching locally and to different countries including Angola and Georgia.

WHO will withhold prequalification of all new products 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 time frame, WHO may consider suspension of the product(s) listed as prequalified from this manufacturing site, and/or may recommend suspension of procurement of all prequalified products manufactured at this site.

Publication of the Notice of Concern

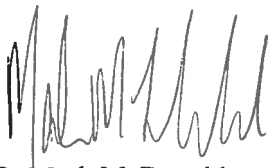
Your attention is drawn to the World Health Assembly Resolution WHA57.14 "Scaling up treatment and care within a coordinated and comprehensive response to HIV/AIDS" of 22 May 2004, which among other actions, requests WHO:

"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 Notice of Concern procedure, WHO may publish this Notice of Concern on its website should acceptable corrective actions not be submitted to WHO within 30 days from the date of this notice. Please note that a Notice of Concern will remain active on the WHO Prequalification Team website until satisfactory corrective actions have been submitted and accepted by WHO.

Should you wish to comment on this Notice of Concern, you are advised to email the undersigned, with details, at prequalinspection@who.int. The matter will be investigated and unless advised otherwise, you can expect to receive a response within 15 working days. All feedback will be treated in confidence and without prejudice.

Yours sincerely,



Dr Mark McDonald
Coordinator
WHO Prequalification Team
Regulation of Medicines and Health Technologies