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Report of the World Health Organization (WHO) Biosafety Inspection Team of the Variola Virus Maximum Containment Laboratories to the State Research Centre of Virology and Biotechnology ("SRC VB VECTOR"), Koltsovo, Novosibirsk Oblast, Russian Federation, 10-15 October 2016

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Report from the World Health Organization Biosafety Inspection of the Variola Virus Maximum Containment Laboratories to the Federal Budgetary Research Institution - State Research Centre of Virology and Biotechnology "VECTOR" of the Federal Service for Surveillance on Consumer Rights Protection and Human Well-being (FBRI SRC VB "VECTOR", Rospotrebnadzor)

Koltsovo, Novosibirsk Region, Russian Federation
10–15 October 2016

EXECUTIVE SUMMARY

The WHO team of international experts carried out a biosafety inspection at one of the two WHO-authorized variola virus (causative agent of smallpox) repositories: VECTOR*, in October 2016 in accordance with World Health Assembly resolution WHA60.1 (2007). [*the Federal Budgetary Research Institution - State Research Centre of Virology and Biotechnology "VECTOR" of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (FBRI SRC VB "VECTOR", Rospotrebnadzor)]

The activities of the WHO inspection team included inspection of the physical high-containment facilities, the supporting engineering systems and the long-term secure specimen storage arrangement and the newly renovated isolation hospital. Before entry into the high-containment facility, the inspection team performed a detailed review of the recent decontamination process. VECTOR completed a self-assessment form to identify updates and modifications after the previous inspection, which provided continuity between inspections. The inspection team had interactive discussions with VECTOR staff, requested and reviewed instruction manuals, standard operating procedures (SOPs), logbooks, meeting minutes, floor plans and other documents.

Management and staff at VECTOR described their institutional commitment to biosafety and biosecurity by delivering detailed presentations of their facility systems and operations throughout the inspection. The team presented and discussed with a representative of Rospotrebnadzor's Central Office and with VECTOR staff their findings of the inspection.

Since the last inspection in 2014, VECTOR has made significant improvements with many previous findings addressed and closed. The inspection team delivered a presentation at the end of the meeting related to the status of the various findings. The inspection team did not note any new findings requiring immediate corrective action (Priority 3) during the 2016 WHO inspection, although they have requested further work on some issues.

In conclusion, the VECTOR repository was found to meet international levels of biosafety and biosecurity for variola virus research and storage. This inspection report places no responsibility on the WHO. Continued safe, secure storage and conduct of work with live variola virus remains the responsibility of VECTOR. The WHO requests from VECTOR an action plan to address the issues noted here for further improvement within 30 days of receiving this report.

CONTEXT

1. There are two authorized repositories of variola virus, namely, FBRI SRC VB "VECTOR", Rospotrebnadzor in Russian Federation and the Centers for Disease Control and Prevention (CDC) in the United States of America. The World Health Assembly resolution WHA60.1 (2007) requests that the WHO maintain inspections of the two laboratories biennially in order to ensure that the conditions of storage of variola virus and research conducted in the laboratories meet the highest requirements for biosafety and biosecurity. In addition, in accordance with resolution WHA60.1, inspection mission reports should be available for public information following appropriate scientific and security redaction.

2. Dates for inspection of both repositories are coordinated with annual maintenance of the facilities, following decontamination. This allows the inspectors to enter areas of the facilities that are difficult to access during the handling of live variola virus. The WHO inspection team, consisting of international experts in a range of fields, visited VECTOR from the 10th to the 15th of October 2016 to meet the biennial inspection requirement of resolution WHA60.1. On the 9th of October, the designated inspectors met for a pre-inspection consultation to review the agenda, inspection practices and inspection protocol.

3. Two representatives of the other repository participated in the inspection as observers, excluding closed discussions among the WHO inspection team and during delivery of the results and recommendations to the inspected repository. This is sharing best practices as well as to ensure parity and impartiality of the inspection.

INSPECTION PROGRAMME

4. By agreement with both repositories, the present inspection included the elements defined in the protocol used in the 2009, 2012 and 2014 inspections. The European Committee for Standardization (CEN) Workshop Agreement (CWA) 15793 (2011) was used exclusively to structure the inspection and to follow up previous "findings". The facilities were not assessed for conformity to the CWA.

5. The inspection team and repository representatives agreed to use a transparent rating scale to categorize the findings at the two repositories. To ensure clarity and a consistent approach, findings are categorized as follows:

- Observations are either positive remarks, including examples of robust controls or other best practices, or related issues that are not directly associated with biosafety and security.
- Priority 1 findings indicate that an improvement is advisable.

- Priority 2 findings indicate that a timely remedial measure is required.
- Priority 3 findings indicate that immediate corrective action is required.

Previous findings found to be ongoing at the next inspection will contribute to the prioritization of future findings and issues to be addressed in any subsequent action plans.

6. VECTOR completed a CWA 15793 clause-by-clause self-assessment (form provided by the WHO before the inspection), which contributed to the audit evidence. The self-assessment was a critical tool in providing for systematic, holistic approach between each inspection and this exercise will likely continue.

7. The inspection took place over six days and included a full one-day inspection of the physical high-containment facility designated for research with variola virus, its supporting mechanical systems, the long-term specimen storage repository and the isolation hospital. Two inspection team members with proof of vaccinia vaccination in the preceding five years to meet internal requirements of VECTOR were permitted to enter the restricted-access, long-term variola virus specimen storage area.

8. The WHO inspection team heard presentations from and held interactive discussions with VECTOR staff. The team specifically requested records, regulatory instruments, institutional rules, instruction manuals, and meeting minutes as necessary for detailed review. The inspection team viewed translated manuals, floor plans of the facility, policies and explanations of the hierarchy of documents. The final day provided an opportunity to discuss and confirm the WHO inspection team's understanding, observations and recommendations, which the inspection team presented to VECTOR.

9. The WHO inspection team made every effort to assess the facility, documents and current practices over a limited timeframe. As the facility was not operational due to scheduled maintenance, the team did not observe any practical work during the inspection. The inspection team appreciated the collaborative attitude and committed engagement of the VECTOR management and all responsible staff throughout the inspection. Presented below are the results of the WHO inspection, the aim of which is to reduce risk and encourage further use of international best practices.

1. Biological risk management system

10. VECTOR representatives presented and provided documentation of the policies, processes and procedures supporting their biological risk management system within their facility. The inspection team overviewed the document hierarchy in terms of national and international regulations, resolutions and their interaction, industry-wide, regional and institutional. The team also examined responsibilities and accountability for biological risk management through a variety of manuals, committee meeting minutes, institutional orders and other relevant documents.

11. The biological risk management system and approval processes of VECTOR integrate senior management, the national regulatory authority and dedicated biosafety committee members, which were demonstrated through the provision of documentation including internal inspection audits for biosafety compliance and training records.

12. *Observation:* VECTOR has shown continual development of a comprehensive management system for work with variola virus, which was emphasised by the provision of up-dated and

translated instruction manuals, examples of biosafety committee meeting minutes and SOPs in accordance with its flow charts.

13. *Observation:* Documentation provided by VECTOR and reviewed by the inspection team incorporated a high degree of cross-referencing and evidence of a robust management system.

2. Risk assessment

14. *Observation:* VECTOR representatives presented their risk assessment process and the hierarchy for review and senior management approval. This included the institutional risk assessment policy, policy and SOPs for handling pathogenic biological agents, and provided evidence of best practice including regular review of SOPs and instruction manuals, workshops and refresher courses.

15. The previous inspection report[1] noted the following ongoing finding (paragraph 23): *"While the administrative controls are clearly defined in VECTOR's risk assessment process, estimation of likelihood and consequence could be further developed. Such enhanced assessment would allow formal comparison and prioritization of risks and of the controls of choice. This would better demonstrate how the organization applies the hierarchy of hazard controls. The inspection team considers this a central safety concept and suggests that it be integrated into the* VECTOR *decision process."* Responsible VECTOR staff formulated proposals on how to improve the risk assessment procedures and controls and how to integrate these into the decision-making process. The Director General (DG) accepted these proposals and implementation included changes to the instruction manual. VECTOR provided the inspection team with a new risk assessment process reflecting likelihood and consequence and demonstrated evidence of its application. This finding is now closed.

16. The previous inspection reported the following finding (paragraph 24):*"The risk assessment process flow diagram defines the intended flow of information. The inspection team suggests that a feedback loop from senior management to the research group be added."* VECTOR made appropriate changes to the instruction manual and presented an up-dated process flow diagram for risk assessment to the inspection team, which included a feedback loop from senior management to the research group. This finding is now closed.

3. Pathogen and toxin inventory and information

17. The inspection team examined the working stock and long-term storage areas for variola virus, viral DNA and genome as well as the instruction manual and logbooks of all materials, which included individuals responsible for the accuracy of the collections. The process for recording and inventorying working and archival collections is well established and controlled, which includes spot checks and a twice-yearly inventory carried out by the staff of the Biosafety Department.

18. The previous inspection report noted (paragraph 28): *"The inspection team recommends that* VECTOR*'s instruction manual clarify the WHO requirements for the transfer of full-length viral DNA more explicitly and state that no site other than the two collaborating centres is allowed to acquire more than 20% of the* variola virus *genome."* VECTOR added clarifications to the instruction manual to reflect the WHO requirements for transfer and the inspection team noted VECTOR's observance of this rule via presentation of the logbooks. This finding is now closed.

[1] Report of the World Health Organization (WHO) Biosafety Inspection Team of the Variola Virus Maximum Containment Laboratories to the State Research Centre of Virology and Biotechnology ("SRC VB VECTOR"), Koltsovo, Novosibirsk Oblast, Russian Federation, 8-13 December 2014

4. General safety

19. The inspection team reviewed aspects on general safety throughout the visit.

20. Previous finding (paragraph 31): *"The current fumigation process has been validated and is verified regularly with biological indicators. The inspection team noted, however, that the current process requires that an operator enter the space during the gassing phase, which is considered to place the personal safety of the operator at significant risk. In the interest of continuous improvement,* VECTOR *is requested to explore alternative, safer methods for the gaseous decontamination process."* VECTOR conducted a series of experiments to explore alternative methods of gaseous fumigation. This identified that less formaldehyde and an improved set-up and delivery procedure could be implemented. The inspection team reviewed an up-dated protocol related to routine decontamination using gaseous formaldehyde and evidence in the form of a modified SOP of improved operator safety. This finding is now closed.

21. Previous finding (paragraph 32): "VECTOR *should ensure that its manuals are updated to reflect changes in policy. For example, they should be updated to reflect the fact that routine use of alcohol burners has been discontinued and they are permitted only with special dispensation if the need arises to open old samples stored in glass ampules."* The inspection team observed an amended instruction manual, which reflected clarity around the restricted use of Bunsen burners. This finding is now closed.

22. *Priority 1 finding*: The inspection team highlighted concern regarding an open wiring method for telephone communication wires (which nominal voltage value does not exceed 12 V) on a panel noted in the laboratory-clothing cloakroom.

5. Personnel and competence

23. VECTOR staff presented the inspection team with information on occupational health and safety, briefings for newly hired personnel, initial workplace, annual refresher and ad hoc training, training records and competency assessment. Training records (employment record books) requested and reviewed by the inspection team were verified for selected individuals.

24. *Observation*: The inspection team found the induction process at VECTOR to be rigorous and extensive.

6. Good microbiological practices

25. VECTOR provided manuals and processes of safe working practices including a comprehensive training programme reflecting a commitment to good microbiological practices, which the inspection team reviewed.

26. The inspection team also reviewed the risk assessment for the introduction of new SOPs for transportation of small animals and the use of sealed buckets in a new centrifuge.

27. Previous finding (paragraph 38): "*The inspection team recommends that* VECTOR *use a method to record microbiological practices (e.g. archived CCTV records) for future inspections, so that the team can verify that they are conducted in accordance with written procedures."* VECTOR highlighted that their captured CCTV footage is a cyclical process that covers a set timeframe to allow for accident and incident investigation. The inspection team therefore recognised that viewing such film footage was not practically feasible as part of the WHO inspections. VECTOR provided

the training regime and detailed SOPs to the inspection team, and highlighted the two-person rule when working in the containment facility. Regular environmental swabbing of the containment laboratory is undertaken and all analysed swabs had been negative. In addition, biosafety staff members undertake periodical monitoring of laboratory CCTV footage. The inspection team considered the combination of these factors satisfactory to close this finding.

7. Clothing and personal protective equipment

28. VECTOR personnel explained in detail the three different categories of personal protective equipment (PPE) for the various areas of the facility. The inspection team observed numerous items of PPE during the on-site facility inspection and a member of the inspection team was given an explanation of the donning and doffing procedures, as the member donned one of the positive pressure suits. VECTOR demonstrated the procedures for suit donning and doffing, testing, use, maintenance, repair and replacement. Details of the procedure for post-use suit decontamination and the processes required for re-use were provided. The inspection team reviewed the logbooks used for signing equipment in and out and for repairs.

29. Previous finding (paragraph 42): *"The inspection team recommends that a better process be used to document suit issues such as tears occurring during use (versus during cleaning and transport)."* The suit-testing logbook was up-dated with additional columns for comments on any tears, decommissioning etc. This finding is now closed.

8. Human factors

30. The inspection team had discussions with VECTOR on this element and the team did not have any concerns relating to human factors.

9. Healthcare

31. The inspection team discussed this element with medical staff during a visit to the newly renovated isolation hospital for highly dangerous infections. This hospital makes it possible to accommodate VECTOR personnel conducting work with variola virus, for quarantine and/or treatment. Discussions included procedures for how potentially exposed staff would enter the facility, caring for staff, the types of equipment including PPE used, and general operation and maintenance of the facility. On this occasion, the team did not have the opportunity to check the engineering system due to scheduled maintenance. It is recommended to take into account extra time for this in the schedules of future inspection visits.