Report of the World Health Organization (WHO) Biosafety and Biosecurity 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, 2 - 7 October 2023
EXECUTIVE SUMMARY

The World Health Organization (WHO) team of international experts carried out a biosafety and biosecurity inspection at one of the two WHO-authorized variola virus (causative agent of smallpox) repositories: VECTOR*, in October 2023 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 maximum containment facilities, the supporting engineering systems and the long-term secure specimen storage and the isolation hospital. Before entry into the maximum containment facility, the inspection team performed a detailed review of the recent decontamination process and documentation. The inspection team had interactive discussions with VECTOR staff, requested and reviewed instruction manuals, standard operating procedures (SOPs) and other relevant biological risk management 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 and observation of the inspection.

Since the last inspection in 2019, VECTOR has made significant improvements and both previous findings are 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 actions (Priority 3) during the 2023 WHO inspection, although they have requested further work to improve some of the biosafety- and biosecurity-related procedures pertaining to variola virus and variola virus nucleic acid work.

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 VECTOR to submit 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. In 2021 and 2022, due to travel restrictions because of COVID-19, the mission needed to be postponed and re-scheduled several times. The WHO inspection team, consisting of international experts in a range of fields, visited VECTOR from the 2 - 7 October 2023 to meet the biennial inspection requirement of resolution WHA60.1. On 1 October 2023, 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 ordinarily participate 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. Unfortunately, due to current circumstances, two representatives of the other repository were unable to participate in the inspection this time.

INSPECTION PROGRAMME

4. By agreement with both repositories, the present inspection included the elements defined in the protocol used in the 2009, 2012, 2014, 2016 and 2019 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 biosecurity.
- 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. The inspection took place over six days and included a full one-day inspection of the physical maximum containment facility designated for research with variola virus, its supporting mechanical systems, the long-term specimen storage 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.

7. 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 manuals, the layout 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 findings, understanding, observations and recommendations, which the inspection team presented to VECTOR top management, senior technical staff and the Rospotrebnadzor representative.

8. 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 collaboration and committed engagement of the VECTOR management team 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

9. VECTOR representatives presented and provided documentation of the legal basis, policies, processes and procedures supporting their biological risk management system within their facility. The inspection team reviewed the documents 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 range of manuals, biosafety committee meeting minutes, institutional orders and other relevant documents (e.g. logbooks).

10. The biological risk management system and approval processes of VECTOR integrate its 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. The inspection team reviewed the documentation of an off-scheduled review conducted by the biosafety department.

11. The inspection team did not have any concerns relating to biological risk management system.

2. Risk assessment

12. VECTOR has a consistent documented risk assessment process in place which considers all potential hazards in a category system followed by decision on commencement of work and considers the risk assessment as a tool for improving procedures. The inspection team has reviewed recent biological and general risk assessments.
13. **Observation**: VECTOR is developing an approach to a risk- and evidence-based biosafety risk assessment.

14. **Observation**: The risk assessment tools provided in the WHO Laboratory biosafety manual, 4th edition, could assist with the continual improvement with considering and recognizing that national biosafety and risk assessment legislation is a priority for VECTOR.

15. The inspection team did not have any concerns relating to risk assessment.

### 3. Pathogen and toxin inventory and information

16. VECTOR presented the requirements and conditions for staff to work with variola virus and the management of the inventoried material before, during and after a research campaign.

17. **Priority 1 finding**: Final destruction of all potentially variola virus DNA-containing specimens and materials regardless of DNA concentration, following sequencing, PCR, microscopy procedures, etc., should be included in VECTOR’s SOPs.

18. **Priority 1 finding**: The existing chain of custody and documentation of transfer of DNA-containing samples and material (including microscopy samples) should be elaborated.

### 4. General safety

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

20. **Previous finding (paragraph 20)**: “As formaldehyde is considered as a probable carcinogen, the inspection team recommends monitoring of formaldehyde concentration in the following situations: on opening steam-formaldehyde sterilizer, inside the pressure suit after steam formaldehyde decontamination, outside containment area in adjacent rooms during the final fumigation, inside containment area 96 hours after final fumigation. The goal is to physically verify (measured) that all critical spots are ventilated sufficiently.”. Formaldehyde monitoring is performed in steam-formaldehyde sterilizer, inside the pressure suit and the suit’s filter and the inspection team reviewed the logbook of the measurements. The finding is now closed.

21. The inspection team did not have any concerns relating to general safety.

### 5. Personnel and competence

22. VECTOR staff presented the inspection team with information on occupational health and safety, documents of the recent annual refresher training and ad hoc training, training records and competency assessment.
23. Observation: VECTOR has a robust and comprehensive training programme in place.

24. The inspection team did not have any concerns relating to personnel and competence.

6. Good microbiological practices and procedures (GMPP)

25. VECTOR provided manuals and processes of safe working practices including a comprehensive training programme reflecting a commitment to good microbiological practices.

26. VECTOR showed that detailed SOPs are in place to ensure GMPP. The re-assessment of the staff handling the variola virus takes place before the work starts and competencies are continually monitored.

27. The inspection team did not have any concerns relating to good microbiological practices and procedures.

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. The inspection team reviewed the logbooks used for signing equipment in and out and for repairs.

29. Observation: Adjustments being made to the positive pressure suits as needed.

30. The inspection team did not have any concerns relating to clothing and personal protective equipment.

8. Human factors

31. VECTOR performs background checks for personnel, continued behavioural monitoring, medical check-ups and provides a multi-level system to resolve work place issues.

32. Observation: Avoidance of blame culture and willingness to report incidents or unsafe condition and behaviours.

33. The inspection team did not have any concerns relating to human factors.
9. Healthcare

34. The inspection team discussed this element with medical staff during a visit to the designated 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. An exercise of an emergency simulation was reported to the inspection team.

35. Vaccination is mandatory every three years for personnel working with variola virus and every five years for all other staff within the facility. Personnel have their antibody titre checked after every vaccination and subsequently every year. A 21-day quarantine period after staff entry into the maximum containment facility is in place, during which travelling is prohibited for longer than one day outside Novosibirsk. Close monitoring of staff health involves annual medical examinations, daily health checks including twice-daily temperature checks for workers and staff associated with the variola programme and entering the maximum containment area. Medical follow-up procedures in case of potential exposure, including differential diagnosis to rule out smallpox, also are outlined.

36. The inspection team did not have any concerns relating to healthcare.

10. Emergency response and contingency planning

37. VECTOR personnel presented their emergency response and contingency planning operations in detail, which are based on national regulations. Civil defence and emergency committee meetings occur regularly and communication exists between local response teams and VECTOR in the event of an emergency. VECTOR personnel receive annual simulation training exercises, covering for example a sudden failure of supply-air to positive pressure suits. Building system contingencies (e.g. back-up power) and reporting schemes during work and non-work hours are in place. In addition, the biosafety committee reviews emergency measures and scenarios regularly.

38. VECTOR has a first responder policy and programme in place and emergency preparedness was assessed for a medical incident through an exercise and the report was shared with the inspection team. The inspection team reviewed emergency response plans, exercises and evaluation of the last 2 years.

39. Previous finding (paragraph 38): “The inspection team suggested a simulation of a medical emergency (e.g. a cardiac arrest) inside and outside the containment area to compare and clarify processes, responding personnel and response times.” VECTOR performed and documented two exercises. The finding is now closed.

40. Observation: Continuation of the practice of carrying out joint exercises with the hospital.

41. The inspection team did not have any concerns relating to emergency response and contingency planning.
11. Accident and incident investigation

42. VECTOR staff presented policies and procedures relating to accident investigation. Since the previous WHO inspection no accidents related to biosafety have been reported. The Ministry of Labour and Social Security of the Russian Federation prescribes the procedure for accident and incident investigation. The VECTOR policies clearly indicate that its staff can report accidents without fear of recrimination. The inspection team reviewed the documentation of an incident investigation.

43. Observation: Robust system for reviewing incidents.

44. The inspection team did not have any concerns relating to accident and incident investigation.

12. Facility physical requirements

45. Before entering the facility, the inspection team checked the fumigation records along with documented results of maintenance and testing during shut down of the facility. Visual inspections of the facility are undertaken twice a year and inspection reports to define any requirements for repair or replacement produced. Since the last inspection there have been renovations to ensure the airtightness of the facility. The airtightness is tested every year before the commissioning of the laboratory.

46. The inspection team did not have any concerns relating to facility physical requirements.

13. Equipment and maintenance

47. VECTOR delivered information related to equipment and technical systems to the inspection team. Biosafety systems, including supply and exhaust ventilation and air supply for PPE, are inspected once every four hours during running time; disinfection and waste treatment systems, transfer units, instrumentation devices, and emergency lighting are inspected on a daily basis. Any deviations are recorded in logbooks and acted upon where necessary. The inspection team viewed the control panel and logbooks within the control room.

48. All equipment, including those for effluent treatment, power supply systems, air supply for PPE, and ventilation units of main supply and exhaust ventilation, those of emergency ventilation and supply and exhaust ventilation in changing rooms, has at least one full redundancy mechanism as a minimum. In addition to two electrical grids from different powerplants, independent back-up power supplies are in place, including generators, in case of power failure within the facility and all are tested on an annual basis. Maintenance work takes place when only research work is not ongoing, unless required in the event of an emergency. Engineering personnel are on standby in case of such an emergency. The inspection team examined relevant logbooks and instruction manuals and the certification of a biological safety cabinet.

49. Observation: The extensive refurbishment is well appreciated.

50. The inspection team did not have any concerns relating to equipment and maintenance.
14. Decontamination, disinfection and sterilization

51. VECTOR emphasized that all decontamination measures are in accordance with the federal resolution “Sanitary and epidemiological requirements for the prevention of infectious diseases” SanPiN 3.3686-21. The staff described in detail the workings of the autoclave, small animal waste treatment, room and pass-through box disinfection and fumigation, and sewage waste treatment. The inspection team examined records of and newly modified SOPs for fumigation, including raw data from biological indicators used to ensure successful decontamination based on the modified procedures. Before entry into the maximum containment facility, the inspection team performed a detailed review of the recent decontamination process and its documentation. In addition, the inspection team observed and discussed the waste sewage treatment, autoclave, animal waste treatment and disinfectant titration systems during the on-site visit of the facility.

52. Observation: For monitoring of the formaldehyde residue in the steam-formaldehyde sterilizer, another column in logbook with the measurement of the formaldehyde in the positive pressure suit’s filter could be added to continue the good practice.

53. The inspection team did not have any concerns relating to decontamination, disinfection and sterilization.

15. Transport procedures

54. VECTOR has established detailed instructions for the packaging, monitoring and recording of material transfers. Transportation of live variola virus does not occur outside the repository facility at VECTOR. Transport procedures for live variola virus and for variola DNA were presented in detail. There are strict rules related to the internal transfer of DNA segments between labs or buildings on the premises of VECTOR, which includes the requirement of approval from the DG, strict and comprehensive documentation and regular checks. The inspection team examined inventory logbooks.

55. Observation: VECTOR demonstrated to the inspection team the airtightness of the metal transport container in addition to its leak-proofness.

56. The inspection team did not have any concerns relating to transport procedures.

16. Security

57. VECTOR described an extensive system for ensuring the physical security, security of material, information security and personnel security based on national legislation and the comprehensive approach to the security assessment. The inspection team had the opportunity to verify various security access layers during the site visit. There is an effective system for securing the archival stocks as well as for protecting sensitive information, data and ensuring the cybersecurity of the facility. VECTOR has developed various documentation covering security risks, which are updated every five years. There are well-documented agreed internal duties and instructions for external authorities as well as procedures for IT personnel and visiting scientists and guests.
58. The inspection team did not have any concerns relating to security.

OVERALL CONCLUSIONS

59. The WHO inspection team found that VECTOR had addressed all of the findings raised from the previous inspection in 2019. The continual efforts and commitment of VECTOR management and staff in ensuring safe and secure processes of work are commendable. The team has made some recommendations from this most recent inspection, which VECTOR should address accordingly to enhance further the safety and security of the facility.

60. The intention of the observations and findings described within this report are to recognize best practices and strengthen further the current measures implemented for the safe and secure management of work on variola virus.

61. In conclusion, there were no major findings observed, however the inspection team recommended some improvements. This inspection report places no responsibility on WHO. Continued safe and secure conduct of work on live variola virus remains the responsibility of VECTOR. As such, the WHO requests that VECTOR propose an action plan to address the issues raised for further improvement. The WHO should receive this action plan within 30 days of receipt of this report.

ACKNOWLEDGEMENTS

The WHO inspection team is grateful for the cooperative discussions held with VECTOR staff as well as their commitment and hospitality throughout the inspection.