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"), Federal Service for Surveillance on Consumer Rights Protection and Human Well-being, Novosibirsk

Koltsovo, Novosibirsk Oblast, Russian Federation
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EXECUTIVE SUMMARY

There are currently two WHO Collaborating Centre repositories that work with smallpox virus; one is situated at the Centers for Disease Control and Prevention (CDC) in Atlanta, USA and the other at the State Research Center of Virology and Biotechnology (VECTOR) in Novosibirsk, Russian Federation.

The inspection was carried out over six days with feedback on the seventh day and consisted of group discussions, review of documentary evidence as well as inspections of the facilities and installations. At the time of the inspection the laboratory was decommissioned for maintenance.

The WHO team observed commendable evidence of commitment to implement the proposed biorisk management system and many areas of good practice during the inspection. A number of findings were identified and observations made for VECTOR's consideration. It is the responsibility of VECTOR to assess and implement associated actions required to address the issues raised.

The facilities can be considered to have an acceptable level of biosafety and laboratory biosecurity for variola virus research and storage. It is requested that VECTOR propose an action plan describing actions and timelines to rapidly address findings.

INSPECTION PROGRAMME

1. World Health Assembly resolution WHA60.1 (2007) mandates WHO to inspect these two centres every two years to ensure that 'the conditions of storage of the virus, and that the

research done in the laboratories meet the highest requirements of biosafety and biosecurity'. In addition, WHA60.1 requests that inspection-mission reports be made available for public information after appropriate scientific and security redaction.

2. In agreement with CDC and VECTOR the inspection protocol used in 2009 was used again for the inspections of 2012. The protocol is based on the publication of the international Laboratory Biorisk Management Standard, which is a consensus Workshop Agreement registered with the European Committee for Standardization (CEN) CWA 15793 (2008).

3. This inspection follows the inspection visit of December 2009. The report of the 2009 visit is available at http://www.who.int/csr/disease/smallpox/Report_2009_VECTOR_WHO_Inspection.pdf.

4. The high containment laboratory (HCL) for work with variola virus has been used for research on this virus since 1996. This is the only laboratory at VECTOR where work with live variola virus is allowed. Storage is restricted to one secure repository where no work with the virus is allowed.

5. The inspection took place over six days, with a presentation and discussion of the findings on the seventh. Both VECTOR staff and the WHO team underlined the serious responsibility they attach to ensuring that conditions of storage of the virus and of research conducted in the laboratories continue to meet the highest requirements for biosafety and biosecurity.

6. In the introductory session on the first morning, VECTOR presented the follow-up actions based on the previous recommendations from 2009.

7. The WHO team reported that a meeting with WHO and representatives of CDC and VECTOR had taken place in Oslo, Norway, between 31 January and 2 February 2012 to review the process for the biosafety inspection visits of the two smallpox repositories. During that meeting agreement was reached on a variety of issues, including the inspection team composition, the draft agenda for the visits, the desire to inspect the facilities when they were accessible to all team members and not in active use to permit evaluation of the laboratory facilities, and how the findings and report would be presented (i.e. a close-out session on the last day of the visit, followed by a written narrative report). The role of representatives from the repository not being inspected (in this case CDC) was identified by the WHO Office of the Legal Counsel to be the one of observers. Observers were able to attend interviews and site tours during the visit, but not discussions regarding findings and key observations, nor were they present at the close-out meeting.

8. The WHO team once again adopted the assessment approach first used during the 2009 inspection visits. The instrument addresses 16 elements relating to laboratory biorisk management. As in 2009, the inspection process consisted of discussions and interviews with key stakeholders, record checks, programme verification, and site inspections. Key findings (areas of nonconformity to CWA 15793) and observations (areas that could benefit from improvement and may become a finding if not addressed before the next inspection visit) were presented for each element on the last day of the visit.

9. Discussions on element 1 (Biorisk Management System) were held on the afternoon of the first day. On the second day the WHO team members visited the high containment laboratory (HCL) and associated animal rooms, the central control room, support rooms for preparation of disinfectant solutions, preparation and storage of positive pressure suits, storage of fragmented genomic DNA, and the waste treatment plant. Only vaccinated team members could visit the repository room and its locked freezers. Discussions on all other individual elements of the assessment protocol were held between the third and sixth day. The WHO team visited the Isolation Hospital of the Medical and Sanitary Unit 163 (MSU-163) on the morning of the sixth day. MSU-163 is dedicated to the management and care of individuals with suspected or actual cases of infection with highly dangerous pathogens.

10. The five WHO team members held closed team discussions on findings over lunch and a brief wrap up session was held at the end of the first and fourth day with representatives of VECTOR.

11. On the afternoon of the seventh day, the findings were presented to VECTOR staff and management, to confirm the WHO team's understanding of initial findings and provide an opportunity to review, discuss and clarify any outstanding issues. During the presentation, VECTOR's Director General requested the team to officially approve work with animals. Further details on this request are provided below.

12. The following sections describe the key findings identified by the assessment team, together with observations providing opportunities for improvement as well as areas considered to represent good practice and noteworthy efforts. The structure of this report follows the 16 management elements addressed within CEN CWA 15793.

13. While a good cross-section of individuals was interviewed, it is emphasized that this was a sample of the organization and activities.

14. The inspection of the laboratory was planned for a time after the laboratory had been shut down and decontaminated to allow for annual maintenance. This provided an opportunity to visit areas that would normally be difficult to access when live virus was being handled. No actual work with variola virus was being conducted at the time of the visit. At the time of the next inspection, the opportunity to observe actual work activities when the laboratory is 'hot' will be planned with VECTOR.

15. In response to the inspection visit and the report, VECTOR is requested to propose an action plan describing actions and timelines to address findings within 30 days of receipt of the final report.

16. In conclusion, the WHO team appreciates the open, collaborative, constructive and highly professional attitude of VECTOR staff engaged in the inspection.

APPLICATION OF THE ASSESSMENT INSTRUMENT

1. Biorisk management system

17. The presence of VECTOR's Director General, together with representatives of the Federal Service for Surveillance on Consumer Rights Protection and Human Well-being, and of the Territorial Department of Regional Branch 25 of the Federal Medical and Biological Agency, demonstrated the involvement of senior management and key regulators in the inspection process. Processes and procedures were found to be well controlled and documented, and responsibilities and accountability for biorisk management was communicated through a variety of manuals, committees, institutional orders, and other relevant documents. Dedicated biosafety staff are widely consulted on activities, and their approval is required for safety-critical issues.

18. Finding – Review and update Instruction Manual to reflect actual current practices

The Instruction Manual referred to some practices and procedures that are no longer routinely followed (e.g. processing glass vials which have been replaced by cryovials). The WHO team therefore recommended a review and update of this and other relevant manuals to ensure that they reflect current practices. It is recognized that some of the outdated practices may need to be returned to under certain circumstances (e.g. glass vials may need to be opened if older stocks were to be used from the repository) and the manual should make it clear that this may require additional / alternative control measures identified through risk assessment, such as additional training or additions to PPE.

2. Risk assessment

Substantial progress on the development of risk assessments was observed, involving a range of individuals, including biosafety staff.

19. Finding – Further develop risk assessment methodology and recording mechanisms

While the work conducted to date is commended, the WHO team recommended introduction of the use of likelihood and consequence measures in the evaluations of risk, as well as a more detailed analysis of individual risks (e.g. stepwise consideration of movement of animals across the corridor; risk of animals wakening during anaesthesia). Recording methods could also benefit from further standardization, in order to provide more detail and make the assessments more transparent to workers and reviewers. Additional detail could also be added in terms of site specific standard operating procedures (SOPs) for work with medium-sized animals, including the use of specific items of PPE (e.g. gloves, aprons, etc. where required) and how these would be decontaminated, together with more detailed evaluation of the use of bioisolators and Class III biosafety cabinets.

3. Pathogen and toxin inventory and information

20. Access to the repository requires both biosafety and scientific staff to be present, and detailed copies of inventory records are maintained

21. Finding – Define materials to be produced during animal work and how they will be inventoried and controlled (e.g. keeping records of inactivated materials)

While evidence was presented to demonstrate that repository stocks were controlled, procedures were not yet in place to inventory and track potentially infectious materials generated during the planned experimental work with animals (e.g. materials for histological examination). The WHO team therefore recommended VECTOR develop and implement mechanisms to identify, track and control all materials containing virus that would be produced during such research campaigns.

4. General safety

22. Procedures are in place to ensure breathing air lines are always in place when using hazardous disinfectants within the containment laboratory, and an on-site laboratory performs regular air quality tests to monitor for the presence of harmful chemicals in other areas (e.g. suit testing room). Noise and light levels are also regularly verified to ensure appropriate working conditions are maintained.

23. Observation – Consider a review to identify relevant standards with regard to performance of emergency shower and eye-wash to ensure installed equipment is fit for purpose

A recommendation in the previous inspection report relating to the need to install an eye-wash station and emergency shower in areas where chemicals were being handled has been addressed. However, in the absence of applicable national standards for this equipment in the Russian Federation, the WHO team suggested to consider a review of relevant international standards and guidelines to ensure appropriate parameters for operation of such equipment have been identified and applied (e.g. water discharge volumes and pressures).

5. Personnel and competency

24. It takes a minimum of one year to be trained to a level whereby workers can gain access to the HCL and work with variola virus. Conditions include one month of general training, and four months specialized training for working safely with group I and II pathogens. A two person rule is applied, together with high levels of mentoring and supervision.

25. Finding – Formalize requirements for work with animals before new activities are introduced

Alternative animal isolators have been installed in the HCL and plans are being developed for work with small and medium-sized animals. Further risk assessment work addressing the potential for contamination of the animal rooms and suits, as well as the minimization of risks of animal bites and scratches should be conducted prior to those activities commencing. However, in preparation for the planned work with animals, the WHO team also recommended conducting training exercises and simulations using lower risk

pathogens or non-pathogenic agents, in order to develop the appropriate skills necessary for the work with variola virus. Conclusions from the risk assessment and simulations should be used to update the Instruction Manual, relevant SOPs, training plans and maintenance procedures.

6. Good microbiological technique

26. A comprehensive training programme is in place to ensure all laboratory workers gain the necessary skills before working in containment.

27. No additional significant findings were identified (see Section 5 above).

7. Clothing and personal protective equipment

28. Rigorous procedures are followed for the decontamination and testing of suits, and a stock of clean and tested suits is maintained and available at all times. Suits of an alternative design to those currently in place are being tested prior to potential approval and introduction.

29. Finding – Summarize hazards and controls associated with suits through a risk assessment

An alternative positive pressure suit model is being introduced. The WHO team recommended that the introduction of this new equipment be subjected to a risk assessment. Areas to be addressed would include an assessment of potential leakage of non-return valves, the performance and reliability of glove / suit connections, and how to decontaminate areas that are potentially difficult to access, including non-return valves.

30. Finding – Review use of gloves

A variety of gloves are available for work in containment. The WHO team recommended a review of the use of latex and nitrile gloves, taking into consideration their potential for tearing as well as for skin sensitization. In addition, the WHO team recommended a review to ensure the proposed use of cotton and chain mail gloves are suitable for the work with animals.

8. Human factors

31. Evidence of good teamwork and communication was observed throughout the visit. In addition, a psychologist and a narcologist (specialist in narcotics) are involved in the regular evaluation of staff. The reporting of incidents and accidents is encouraged, and no blame was reported to be attached to incidents reported.

32. No significant findings were identified.

9. Healthcare

33. Good practices were observed, including routine annual medical examinations and daily health checks for workers. HCL staff with access to variola virus are vaccinated every three years, and engineering / technical staff working on the building are vaccinated every five years.

Upon completion of work with variola virus during a campaign, scientists must respect a twenty-one day observation period before they are allowed to travel.

34. Observation – Ensure effectiveness of controls over potential contamination from patients in the isolation hospital

It was unclear how potential aerosol and resulting surface contamination (e.g. on suits) would be adequately controlled between patient rooms and adjacent spaces. Room air changes were reported to be relatively low (three per hour) in comparison to those in the HCL and this would result in a potentially prolonged period during which staff would be unable to remove respiratory protection after visiting patients in their rooms, given the likelihood of contamination of this area (due to air flow dynamics and door opening / closing). The WHO team recommended that this area be subject to a risk assessment to demonstrate that applied measures are effective in controlling the extent of surface and air-borne contamination beyond patient rooms. With regard to the spaces adjacent to patient rooms (e.g. where medical and support staff remove their PPE), the assessment should address the required air clean-up time required before staff can remove their respiratory protection and how surface and suit decontamination can be controlled. This assessment should be documented and the findings used to inform engineering and management controls.

10. Emergency response and contingency planning

35. A building-specific incident response plan has been developed that addresses the scenarios identified in the CWA document. Emergency drills and simulation exercises were reported to be run annually with lessons learnt feeding into the incident plan.

36. Finding – Consider whether all relevant local emergency scenarios are addressed in relation to work with animals

With the reintroduction of work with animals, the WHO team recommended further consideration of emergency scenarios that may be relevant, including the possible escape of animals from cages and animals regaining consciousness during anaesthesia.

11. Accident/incident investigation

37. No accidents or incidents were reported for the period since the previous WHO inspection visit. The procedure for accident and incident investigation is prescribed by an executive order of the Ministry of Labour and Social Development. This procedure addresses accidents leading to actual harm and involves the full investigation of an external agency. The identification of suit damage also triggers a detailed investigation.

38. Observation – Examine further opportunities for development of accident / incident reporting systems in terms of collecting and analyzing data from incidents in line with good practices described in the CWA

The WHO team recommended VECTOR explore the possibility of improving the system for collecting and analyzing data from incidents and near-misses (i.e. events not necessarily associated with actual harm) in line with good practice described in CWA 15793.

12. Facility physical requirements

39. A high standard of surface finishes were observed in the effluent treatment room and improvements have been made to the vivarium since the last inspection visit.

40. Finding – Ensure all finishes are maintained in a condition to allow for adequate cleaning and decontamination

Work has been carried out to improve surface finishes in the HCL since the previous visit (e.g. repainting). However, areas for improvement were noted, including flaking paint, cracks in insulation casings on pipework (the latter were reported to have been rectified during the visit), and unsealed wooden finishes observed in one room. The WHO team recommended that the maintenance and inspection programme be reviewed to ensure all surface finishes are maintained in an optimal condition to allow for effective cleaning and decontamination, and that the standard observed in the effluent treatment room (e.g. smooth walls and other surfaces) be used as a benchmark against which all surface finishes throughout the HCL be measured and approved.

13. Equipment and maintenance

41. A dedicated maintenance team and schedule are in place with 24/7 cover. Critical equipment is supplied using systems providing multiple levels of redundancy, including a diesel generator.

42. Finding – Areas and equipment not being used should be subjected to an adequate cleaning and maintenance regime

Not all the rooms within containment are currently being used during research campaigns. The WHO team recommended that any rooms, areas and equipment that are not used but connected to the central ventilation system as an integral part of the containment area, be subjected to an adequate cleaning and maintenance regime. This should adopt standards comparable to those applied to rooms and equipment in use, so as to ensure unoccupied areas remain clean and in a condition whereby they can be adequately decontaminated (e.g. free from dust build-up).

14. Decontamination, disinfection and sterilization

43. Comprehensive procedures are in place for the decontamination of suits, including scrubbing with chemical disinfectants and formalin autoclaving after every use. Disinfectant efficacy has been validated and kill curves were shown. A revalidation of formaldehyde decontamination procedures is planned for the model of positive pressure suites currently being evaluated for introduction.

44. Finding – Review the decontamination process for the animal isolators

New containment units (bioisolators) have been installed to maintain small animals in isolated and filtered cages, and medium-sized animals in non-filtered, fenestrated non-human primate cages. While this approach will significantly reduce the spread of infected aerosols during animal holding, the rooms will be challenged with infected aerosols produced during animal procedures and husbandry. The WHO team recommended to conduct a risk assessment of the decontamination process for these bioisolators, PPE and the surrounding area (including the corridor and duct work) in order to ensure adequate decontamination can be carried out, ensure material compatibility with proposed disinfectants, replace any mechanical parts that may prove difficult to clean (e.g. foam insulation material in housing), and address other potential hazards associated with use of this equipment.

15. Transport procedures

45. Procedures for the packaging and transporting of live variola virus and DNA are well established. VECTOR reported that there has been no external transport of samples of live variola virus since the last inspection visit of 2009. Currently, no variola virus or DNA is stored within the containment laboratory.

46. Finding – Finalize transport procedures for medium-sized animals

The transfer of medium-sized animals into and out of the bioisolators, and into and out of biosafety cabinets will result in challenges in maintaining containment provided by these devices. In addition, the transport of medium-sized animals from the holding room to the necropsy room or other rooms occurs across a corridor. The WHO team recommended to conduct a risk assessment and ensure all animal transport procedures are adequately controlled.

16. Security

47. Independent security services are provided by the Ministry of Interior. Strong security measures involving physical, information and personal security measures were described and it was reported these are strictly followed. In addition to the controlled and strictly documented access to sensitive materials, seals are used to secure materials in freezers and incubators. An additional area of good practice noted was the advance review of research projects to identify potential issues with data produced.

48. No significant findings were identified.

Work with small animals

49. The WHO team was provided with an assurance that risk assessments, procedures and associated training are in place for small animals, and these have been used extensively for work with other dangerous pathogens (e.g. Marburg, Ebola).

50. Regulatory approval has already been sought and granted for the proposed variola virus work with small animals.

51. Since no significant issues were identified with the biorisk management issues associated with the proposed small animal work, the inspection team will recommend to WHO senior management to support VECTOR's proposal to commence work with small animals.

Work with medium-sized animals

52. Provided existing controls are implemented and further risk assessments are conducted as described in this report, the WHO team sees no reason why the work with mid-sized animals in containment should not proceed once the identified controls from the risk assessment have been used to update the Instruction Manual, training plans, relevant SOPs and maintenance procedures. Relevant national and local approvals should also be received prior to commencement.

53. The recommendations of the inspection team must be validated by WHO senior management, including the degree of assurance required regarding close-out of any actions identified.

OVERALL CONCLUSIONS

54. In relation to the inspection of 2012, the WHO team found that improvements had been made and that the recommendations of the previous report had been addressed.

55. The WHO team acknowledged VECTOR's proactive efforts to implement a biorisk management system aligned with the CWA 15793. Commitment and engagement from management and all staff involved was evident. The WHO team welcomed acceptance by VECTOR of new concepts and measures taken to further improve existing systems and practices.

56. The WHO team acknowledged the presence of dedicated, committed and knowledgeable professionals that created a professional and constructive atmosphere during the inspection with proactive participation in discussions and activities.

57. This inspection report places no responsibility on WHO for the safe conduct of work that uses live variola viruses in this facility, which remains the responsibility of VECTOR.

ACKNOWLEDGEMENTS

The WHO inspection team was grateful to VECTOR for the cooperation, commitment and hospitality during this inspection.