World Health Organization

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

Kol'tsovo, Novosibirsk Oblast', Russian Federation
30 November – 4 December 2009

EXECUTIVE SUMMARY

The WHO Inspection Team visited VECTOR in order to conduct an inspection of one of the two authorized repositories of live variola virus with the aim of ensuring that the conditions of storage of the virus, and that the research done in the laboratories meet the highest requirements of biosafety and biosecurity, as mandated by the World Health Assembly in resolution WHA60.1. That same resolution also strongly reaffirmed the decisions of previous World Health Assemblies that the remaining stocks of variola virus should be destroyed. The team, in agreement with VECTOR, used a new Laboratory Biorisk Management standard for the assessment. The protocol used was based on the CWA 15793 Biorisk Management Standard.

The WHO inspection team was satisfied with the security and safety arrangements for maintaining, and working with, live variola viruses within the Maximum Containment BSL-4 (Biosafety Level-4) Laboratory and its associated facilities. The VECTOR BSL-4 facility was assessed to have the capacity to conduct work safely with live variola virus as it stands.

Although a number of recommendations have been made, the WHO inspection team found that VECTOR implements appropriate levels of biosafety and biosecurity for its work with variola virus.

A positive finding was that VECTOR staff recognizes the need for a policy and process of constant improvement of biosafety and biosecurity systems at VECTOR.

The WHO inspection team recommended that VECTOR staff collaborate with CDC (Centers for Disease Control and Prevention) staff and WHO experts in order to establish a tool for future WHO biosafety inspections of the two repositories based on the CWA 15793 Biorisk Management Standard.

In summary, the WHO inspection team found the VECTOR Maximum Containment BSL-4 facility to be safe and secure for the work with live variola virus.

CONTEXT

1. The WHO inspection team visited the State Research Centre of Virology and Biotechnology VECTOR in order to conduct an inspection of one of the two authorized repositories of variola virus. The team also inspected the facilities of the Medical and Sanitary Unit 163 of the Russian Federal Medical and Biological Agency, which provide medical coverage and emergency response capabilities for staff working in VECTOR's Maximum Containment laboratories.

2. The aim of the visit was to ensure that the conditions of storage of the virus and the research done in the laboratories meet the highest requirements of biosafety and biosecurity, as mandated by the World Health Assembly in resolution WHA60.1. That same resolution also strongly reaffirmed the decisions of previous World Health Assemblies that the remaining stocks of virus should be destroyed.

3. Staff from VECTOR had participated in the WHO inspection of the Maximum Containment Facility at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, United States of America, in March 2009. To maintain parity through the use of a common set of criteria for the inspection, the WHO team agreed that the new Laboratory Biorisk Management standard, developed through the European Committee on Standardization (CEN) and which had been used in the CDC inspection, would also be applied in the inspection of the maximum containment facilities at the VECTOR centre.

INSPECTION PROGRAMME

4. The inspection took place over four days, with a presentation and discussion of the draft report on the fifth day. Both VECTOR staff and the WHO team stressed their commitment to the safety of the researchers and other workers in the facility and to ensuring, as noted in resolution WHA60.1, that the conditions of storage of the virus and for research conducted in the laboratories fully met the requirements for biosafety and biosecurity.

5. It was also noted that, as in the case of the report of the inspection team of the CDC facility and in accordance with resolution WHA60.1, the final report of the team would be made public, after redaction for scientific clarity and consideration of security issues.[1] The timing of the visit was important not only in view of the imminent review of research on variola virus in 2010 for the report to the Sixty-fourth World Health Assembly in 2011 but also the close scrutiny being given by WHO's Member States to the public reports of the inspection team.

6. The WHO team introduced the assessment instrument, whose aim was to assess biosafety and laboratory biosecurity, thereby increasing transparency, consistency, objectivity and reproducibility in the inspection process. The tool comprises 16 elements concerning management of biorisk, and the team also addressed a specific element on variola virus research. The process consisted of discussions, interviews, programme verification (for instance, checking of records and documentation) and site inspections.

[1] Resolution WHA60.1, operative paragraph 4(5).

7. Visits were made to several locations on the site of the Maximum Containment laboratories before the team reconvened for discussions. The fourth day included a visit to the dedicated isolation hospital of Medical and Sanitary Unit 163, which has its own suite of laboratories. The hospital is located on the site and is designed for the management and care of individuals with suspected or actual cases of infection with highly dangerous pathogens. On the fifth day a draft of the report was presented for review and comment.

8. VECTOR staff recognized that, as the assessment instrument was generic, it could and should be adapted to the needs of the Russian federal authorities. Proposals to improve and harmonize inspection procedures would be welcome. In this regard it was proposed that, following the experience of the inspection of the CDC facilities earlier in the year and the present inspection, a structured document on the principles of organizing and conducting such inspections be prepared.

GENERAL COMMENTS

The WHO inspection team was extremely impressed by the consistent and substantive involvement of senior-level management of VECTOR in the entire WHO inspection, reflecting a genuine commitment to continually improve institutional biosafety and biosecurity. In particular the team noted the extensive involvement of the Director-General and the presence of representatives of the Federal Service for Surveillance on Consumer Rights Protection and Human Well-being (Rospotrebnadzor) and of VECTOR's external oversight body (the Territorial Branch of Regional Office 25 of the Federal Medical and Biological Agency).

9. It was clearly stated that relevant Russian federal regulations and rules were paramount to the operation of VECTOR's research work.

10. The inspection team complimented VECTOR on its response to previous recommendations, including the improvements on clear signage of the facilities and to the overall treatment of the flooring and walls within the Maximum Containment Laboratory.

APPLICATION OF THE ASSESSMENT INSTRUMENT

Biorisk management system

11. The WHO inspection team noted that both VECTOR and CDC accepted the use of the CWA 15793 Biorisk Management Standard as an applicable standard, but that both institutes feel that its application in the inspection process can be improved. The team therefore recommends that VECTOR staff collaborate with CDC staff and WHO experts familiar with the Standard in order to establish a tool for future WHO biosafety inspections of the two repositories. Such a tool would clarify documentation, procedural, and/or other requirements for each facility before and during future WHO inspections.

12. The system of documentation was found to be both comprehensive and well maintained. Records examined were well maintained, comprehensive and up to date.

13. According to an existing procedure, members of staff prior to starting work at VECTOR sign that they have read and understood the relevant regulations and instructions.

14. Rospotrebnadzor and VECTOR continue to give strong emphasis to training on biosafety. On the VECTOR site, there is a dedicated unit and facility, and training staff have developed their own audio-visual material (see paragraph 25 below). Specific additional programmes for biosafety specialists (for example on decontamination of rooms) are being designed for staff members working in the relevant buildings of VECTOR. All such courses are based on six seminal documents: the

- *WHO Laboratory Biosafety Manual*, 3rd edition, 2004;
- five Russian Federation regulations, including the Federal Law on Human Sanitary and Epidemiological Welfare dated 31.03.1999;
- Sanitary Rules SR 1.3.1285-03 "The safety of work with microorganisms of I - II pathogenicity (hazard) groups";
- Sanitary Rules SR 1.3.2322-08 "The safety of work with microorganisms of III - IV pathogenicity (hazard) groups and agents causing parasitic diseases";
- Sanitary Rules SR 1.2.036-95 "The order of accounting for, storage, transfer and transportation of microorganisms of I-IV pathogenicity groups";
- Sanitary and Epidemiological Rules 1.2.1318-03 "The order of issuing a sanitary and epidemiological conclusion on the possibility of conducting work with agents of I-IV pathogenicity (hazard) groups, causing human infectious diseases, with genetically modified microorganisms, poisons of biological origin, and helminths".

Other courses, including recent ones on influenza (H1N1) 2009, contain large elements on biosafety. The WHO inspection team was informed that VECTOR is currently reviewing rules and guidance on biosafety issued in Canada, the United States of America, the United Kingdom of Great Britain and Northern Ireland and by WHO.

15. The Territorial Branch of Regional Office 25 of the Federal Medical and Biological Agency of the Russian Federation acts as an external oversight and regulatory authority. It receives copies of the programme of work with variola virus in advance of any work being undertaken in VECTOR and then draws up a schedule of (unannounced) biosafety audits. Its report and recommendations are sent to the Director-General of VECTOR.

16. The facility is subject to inspections by VECTOR personnel (internal inspections) and also by Regional Office 25 (external inspections). Inspections and audits were found to be well planned and structured, with structured reporting and closing out of any issues raised. The representative of Regional Office 25 informed the WHO Inspection team of the fact that no accidents or incidents have occurred during VECTOR's work with variola virus and that the setup of work and ensuring biosafety compliance in handling this virus is in accordance with the applicable national legislation.

17. The head of each department receives a copy of the manual on organization and performance of work with variola virus in the Maximum Containment BSL-4 Laboratory, approved by the Director-General, and has the responsibility for making all his or her staff aware of its contents. There are indications that this responsibility is fulfilled; indeed the information forms the basis for annual and more frequent refresher courses and examinations.

18. Before any research work on variola virus can be performed, biosafety requirements are specified in official documentation (reports on tests performed on engineering biosafety systems; the order on convening a committee on biosafety knowledge assessment; records of knowledge assessment by the committee; and the order on personnel work authorization and initiation of work with variola virus). Copies of the documents were seen by the WHO inspection team.

Risk assessment

19. The "Explanatory Letter" sent to Rospotrebnadzor is equivalent to a biosafety assessment. This letter details the level of training of personnel, personal protective equipment and clothing required, and the movement of infectious material. It is linked to a specific organism and laboratory. If any condition changes VECTOR submits a new explanatory letter. The permission is called the Sanitary-Epidemiological Conclusion, which provides specific permission to work with variola virus.

20. In addition to complying with Rospotrebnadzor's mandated policies, VECTOR has also produced a risk assessment document on the work with variola virus. The inspection team considered this to be an excellent initiative; it commended VECTOR for its efforts and encouraged it to develop risk assessment approaches further. Potential areas for application could include the forthcoming move of the repository, work with animals and security-related assessments.

Pathogen inventory and information

21. Preparations for the transfer of the collection of stocks of variola virus and variola viral DNA into the building containing the Maximum Containment BSL-4 facility in January 2010 have been made.

22. Data were reported on the variola virus collection at the VECTOR centre.

General safety

23. *Chemical safety.* The WHO inspection team noted that the entrance to the chemical storage area was appropriate in the areas for preparation of the disinfectant, and that chemical protective clothing was available. However it was suggested that further consideration should be given to adding the following safety measures, complementary to Russian regulations. Facilities for washing eyes and emergency water showers to remove chemicals through accidental contact should be provided, and these facilities should be regularly tested to ensure proper working order. Stock chemical canisters should be stored away from preparation areas and isolated above the floor, in case of flooding or

spills. The working procedures and equipment used by the staff testing caustic solutions should be periodically reviewed by senior supervisors.

24. The two-person rule is observed at VECTOR and in the isolation hospital unit in MSU 163.

Personnel and competency

25. A specific unit in VECTOR undertakes modular methodological training programmes, which are approved at Rospotrebnadzor. It runs a four-month postgraduate diploma course on the theory and practice of working with highly dangerous pathogens, and a 72-hour programme specifically on biosafety (when run recently, the course included high-level speakers from WHO and relevant Russian Federation agencies). Staff have to attend periodic refresher courses, and undergo annual testing and certification for their knowledge of procedures and regulations; the results are included in the staff member's personnel file. All members of staff are informed about the health hazards relating to infection with dangerous pathogens and the necessary responses. A further examination is given to staff members who use protective suits. The highest level of training in biosafety in the country, both theoretical and practical, is that given at VECTOR.

26. Among their responsibilities, information technology personnel ensure security of data and protection against hacking and other attempts to obtain electronic information. They train and develop their expertise at both VECTOR and other locations.

Good microbiological technique

27. Although it appears that good microbiological practices pertain, the team had no opportunity to examine this aspect. However, the team did see training manuals and a BSL-2 training laboratory.

Clothing and personal protective equipment

28. The team was informed of the fact that new positive-pressure suits will be introduced within the next two years. The currently-used positive-pressure suits are robust and the team looks forward to inspecting the Russian-designed replacements.

Human factors

29. Supervisors monitored staff for behavioural and psychological characteristics, and every five years staff are examined by a behavioural psychologist. A collective approach is applied towards breaches of working practices; any such incident is discussed by the team and the whole team has to have its knowledge of working practices reviewed. Any major breach of practice is analysed and the results are transmitted to all equivalent institutions in order to prevent any recurrence. In order to encourage openness and transparency, staff are not administratively punished for technical breaches that resulted in an accident. Staff demonstrating good practice may be rewarded. In the case of a staff member who makes repeated errors in laboratory practice, however, dismissal is possible.

Health care

30. In the case of a member of staff who fails to report for work or is absent for more than two hours, VECTOR's rules specify the actions that have to be taken to investigate the incident. This provides an additional means of raising awareness among staff.

31. The inspection team was provided with reports of VECTOR having access to, and in some cases using, new approaches to vaccinating against smallpox. These methods would be of significant interest to the larger world health community, and the inspection team encourages the responsible authorities to publish the available data relating to the safety and efficacy of these new smallpox vaccines.

32. The inspection team reviewed the special medical facilities that are available for housing potentially infected personnel. It was confirmed, by both MSU-163 and VECTOR staff, that all smallpox diagnostics will be performed under BSL-4 containment. The inspection team asks that a statement be provided to WHO saying that this smallpox diagnosis strategy will be recognized as being performed by an accredited body and the results of such work (confirmatory identification) would be legally acceptable to the Russian public health authorities.

33. It was confirmed that, in order to minimize any potential contamination of healthcare providers by patients potentially exposed to variola virus, health-care providers would exit from the patient area to the adjacent room in a unidirectional (i.e. one-way) manner. That is, health-care providers will not return to the patient area after exiting into the adjacent room where they decontaminate and remove their pneumatic (positive-pressure) suits. This one-way direction of travel of health-care providers is an acceptable procedure for infection control, as it minimizes the potential for infection of non-infected personnel in adjacent areas. The team did not have an opportunity to view the facility under operating conditions, or with the air handling system operating, but it was confirmed that the patient areas exhibit the greatest pressure differentials when in operation.

Emergency response and contingency planning

34. The team was informed that procedures are documented for responses to an emergency, and reviewed the texts.

Accident and incident investigation

35. All accidents have to be reported, by law. An algorithm for the obligatory investigatory and reporting process forms part of the training programme and was seen by the inspection team. Once the incident is reported, its seriousness is determined and the response is graduated accordingly.

36. A formal accident-investigation process is in place with investigations carried out by an external commission, structured reporting forms and other good practices. There

are additional examples of good practice related to this area, including internal occupational health and safety inspections, and the opportunity to send memoranda regarding potentially dangerous situations. It was also recognized that there may be further opportunities for development of systems in terms of collecting and analyzing data from incidents in line with good practices described in CWA 15793, and the desire to continue to consider such approaches and to continual improvement in general is commended.

Facility physical requirements

37. The WHO inspection team commends VECTOR on the state of the floors in the facility, and noted the fresh painting of walls and ceilings.

38. The inspection team reviewed the systems used to monitor airflow and pressure gradients in the MCL (Maximum Containment Laboratory; BSL-4). These systems are located in the control room where their operations are reviewed by regular staff logging in prior to entering the MCL. The inspection team believes that it would be a further convenience for these staff, if additional systems (e.g. magnehelic gauges) were to be installed at the MCL entry points during the course of regular maintenance and upgrading. This would provide staff with an immediate opportunity to confirm the pressure differentials.

Equipment and maintenance

39. The inspection team examined the animal facilities within the MCL. These facilities can permit some flow of air between different housing areas and thus create a potential for cross-contamination of experimental animals. To minimize the risk of unexpectedly altering the distribution of infection, the inspection team recommend that all animals be further contained within High Efficiency Particulate Air (HEPA) filtered (or equivalently filtered) isolation cages. These cages should also be used to transport animals between procedure and holding rooms and thus prevent any direct exposure of laboratories, corridors and personnel within the maximum containment facility to materials shed by infected animals. The inspection team also recommended that these methods be extended to the necropsy suite, where any manipulations must be performed within a containment device (e.g. a Class II biosafety cabinet) designed to minimize the spread of materials from infected animals into the surrounding laboratory areas.