Report of the World Health Organization (WHO) Biosafety Inspection Team of the Variola Virus Maximum Containment Laboratories to the Centers for Disease Control and Prevention (CDC)

Atlanta, Georgia, USA, 2-6 March 2009

EXECUTIVE SUMMARY

The WHO Inspection Team visited CDC 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. The team, in agreement with CDC, used a new Laboratory Biorisk Management standard for the assessment.

At the beginning of 2009, CDC operationalized a new maximum containment laboratory for work with live variola virus. Stocks have been transferred from the existing maximum containment BSL-4 laboratory building. The original laboratory is being maintained.

The WHO inspection team was satisfied with the security and safety arrangements for maintaining, and working with live variola viruses. The CDC Maximum Containment 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, no issues compromising safety or security were identified during the assessment.

A positive finding was the recognition of the need for a policy and process of constant improvement of biosafety and biosecurity standards.

The WHO Inspection Team found the new assessment protocol to be a useful methodological tool for standardizing the WHO biosafety inspections of the variola virus repositories. It contributes to better structuring of the process, making it more objective. It is proposed to use the protocol as a methodological framework for conducting such inspections in the future.

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

CONTEXT

1. The WHO inspection team visited CDC in order to conduct an inspection of one of the two authorized repositories of 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 virus should be destroyed.

2. In a previous inspection of CDC's facilities, in October 2005, the WHO inspection team found satisfactory security and safety arrangements for storing and working with CDC's collection of variola virus stocks within the single maximum containment laboratory in an existing building. The team had been informed of the planned move into a new biosafety level 4 (BSL-4) laboratory, then under construction.

3. The team had also informed CDC that WHO intended to develop a standardized method for evaluating biosafety and biosecurity at the two repositories. A new Laboratory Biorisk Management standard has been developed through the European Committee of Standardization (CEN) (ftp://ftp.cenorm.be/PUBLIC/CWAs/workshop31/). In agreement with CDC, the assessment visit would be carried out based on this new standard.

4. At the beginning of 2009 the new maximum containment laboratory for work with variola virus work was operationalized. Stocks have been transferred from the existing maximum containment BSL-4 laboratory building. The old laboratory is being maintained.

INSPECTION PROGRAMME

5. The inspection took place over four days with a presentation and discussion of the draft report on the fifth day. Both CDC staff and the WHO team underlined the serious responsibility they attached to ensuring that conditions of storage of the virus and of research conducted in the laboratories meet the highest requirements for biosafety and biosecurity.

6. In the introductory session on the first morning, the WHO team noted that resolution WHA60.1 addressed two critical concepts: ensuring that the conditions of storage and research meet the highest requirements for biosafety and biosecurity, and that the reports of the inspection missions should be available for public information after appropriate scientific and security redaction.

7. CDC staff reviewed the status of the facilities, indicating that the repository continues to be stored in two locations. Training protocols for work in the new facility had been designed and a new governance structure put in place. The recent national Select Agent legislation covered all work on live variola virus.

8. The WHO team introduced the new assessment approach that had been designed for assessment of biosafety and laboratory biosecurity, which should ensure transparency,

consistency, objectivity and reproducibility in the inspection process. The instrument addressed 16 general elements on laboratory biorisk management and the WHO team also addressed an additional specific element on variola virus research. The process would consist of discussions and interviews, programme verification (for instance, checking of records and documentation) and site inspections.

9. CDC staff outlined the executive and managerial hierarchy of the agency and, in discussion, described the "incident command structure" for various types of incident and indicated that there existed a clear separation between programmatic and support services.

10. Visits were made to a number of locations on the site before reconvening for discussions on the individual elements of the assessment instrument, discussions that continued during the second and third days. The fourth day consisted of visits by the WHO team members to several facilities including the neighbouring special care unit designated to accept suspect and verified smallpox cases for high containment emergency care in case of need. On the fifth day, the draft report was presented to CDC staff for review.

APPLICATION OF THE ASSESSMENT INSTRUMENT

11. Both the WHO team and CDC staff recognized that the nature and application of the assessment approach would evolve with experience and evaluation.

Biorisk management system

12. CDC staff informed the WHO team that CDC had an overarching policy on health and safety issues, for which the Director of CDC was responsible. Policy was further defined at the laboratory level, with Principal Investigators holding responsibility in compliance with a written policy on the reporting of incidents implemented by the Office of Health and Safety. The WHO team noted that Laboratory Manuals for each facility existed and that researchers had to indicate that they had read the guidance on safety procedures. The risk assessments relevant to “site-specific” particular practices in the laboratory are filed in the operations manual, separate from the laboratory standard operating procedures. The WHO team strongly welcomed the inclusion of a commitment to continued improvement in the written policies. The WHO team recommended that the policy should be reviewed in order to ensure that formal mechanisms are set in place to reinforce the commitment from senior management to biosafety and biosecurity as key CDC activities.

13. Although it was mentioned that safety was a component of individual scientists’ annual performance reviews, no documentation/evidence was provided/presented that specif objectives and targets with regard to biorisk control were being set in place, nor that these were being incorporated into individual job descriptions and management mechanisms. The need to improve the control of documentation (see below) was recognized by CDC and this is an area where objectives and targets could be set by management. Other areas for consideration could be the completion of more precise risk assessments for key areas and operations (e.g. use of dunk tanks) and the need for vaccination of personnel. The WHO team recommended that consideration be given to setting formal objectives and targets for continuous improvement of biorisk management. It also recommended specific identification and integration of roles and

responsibilities, and follow-up of the use of committees, terms of reference, minutes and other such mechanisms, and how these tie in with policy requirements.

14. Control of documents and records depended on different policy frameworks. Within CDC each policy had an owner responsible for its review. CDC informed the WHO team that the Select Agent legislation specified compliance with specified norms on documentation which was reviewed every two to three years. CDC has procedures for managing and protecting sensitive information which is designated as controlled unclassified information (CUI), with rules about version and content control. Current policy does have specific procedures for the labelling and handling of this information and once national guidance on CUI is codified, CDC will harmonize existing procedures with that guidance. It appeared, however, that documents are not classified in terms of their control status, and there is no system for ensuring that there is consistency in terms of the manner in which documents will be handled with regard to document control. Examples of documents examined that should be included in such a policy would include standard operating procedures, security information, safety manuals, audit and inspection checklists. The WHO team recommended that consideration should be given to the need for effective mechanisms to identify and control documentation associated with the variola virus research programme, including support groups. CDC should review the requirements for contractors and other associated personnel and consider data collected, its potential use and sensitivity, and mechanisms whereby it can be retained and identified in line with need.

15. The range of data collected is wide, and includes records of workers in various areas, medical data such as vaccination and health checks (to which strict rules of confidentiality are applied), mechanical performance information, environmental data, and scientific data. Personal medical records were kept for up to 30 years and for other data national criteria for storage applied, for instance the Select Agent legislation which specified three years storage. Access logs could be kept indefinitely. The electronic inventory of viral stocks, now four years old, was updated weekly and verified annually. The WHO team was informed that one incident could give rise to several reports, depending on the offices involved, but that for reporting under the Select Agent legislation these were combined into a single report.

16. It was also noted that the variola virus research programme staff were already heavily committed to their existing duties, and that the implementation of supplemental biosafety and biosecurity improvements will require additional effort on the part of CDC to complete effectively. In terms of budgeting for biosecurity issues, resources needed to be secured and provided where necessary to ensure sufficient time, staff and other resources required, and to allow completion of this work without unduly affecting the research programme.

17. The agency continued to give strong emphasis to training, with additional elements added to the training plan as needed. The Office of Health and Safety conducts a comprehensive annual health and safety survey programme using a checklist to address management issues and physical conditions. However, a different approach is applied to the BSL-4 facilities. The WHO team commented that the comprehensive survey is a good practice and recommended that consideration be given to increase harmonization of audit practices between the BSL-3 and BSL-4 laboratories, including the variola virus research programme.

18. Some good examples of inspections and audits were presented, including daily checks of working areas. However, there did not appear to be an overall audit and inspection plan, which included definition of competency requirements for auditors, mechanisms for approval and how actions will be identified and closed out. External staff, in collaboration with CDC staff working with variola virus, conducted audits of locations, agents and risks and inspections every two to three years under the Select Agent requirements. The WHO team recommended that internal audit processes be reviewed and that a comprehensive system be developed that included terms of reference for inspection and audit in order to specify details such as frequency, independence of auditors and how the results would be reported and issued.

19. The roles, responsibilities and authorities with regard to variola virus were explained. Safety was everybody's concern, with final responsibility resting with the Director of CDC, but the roles were separate for health and safety, building services, security and emergency preparedness and programmatic aspects. All were represented in the High Containment Laboratory Operating Group (HOG), which provided a mechanism for management, responses and training. Key documents constituting the operational structure command and control structure included the HOG's charter and the Biosafety Manual. It was acknowledged that the new building would need a new model, and the Group provided the framework. The HOG identified responsible individuals for training needs and was the forum for discussion about operational aspects.

20. The US Army Medical Research Institute of Infectious Diseases (USAMRIID) had signed a memorandum of understanding with CDC and had requested permission for up to ten researchers to work in the containment laboratories. A Statement of Work had been signed under whose terms USAMRIID researchers were committed to observing all CDC's biosafety and biosecurity practices and standard operating procedures.

21. A visit to the neighbouring emergency care facility revealed facilities and procedures prepared to handle suspect cases. The WHO team recommended that CDC should review the protocols for the containment of variola virus-infected persons in place.

Risk assessment

22. CDC staff described a range of approaches and policies, from specific policies for approval of new research including work with animals (through, for instance, the Institutional Animal Care and Use Committee), job hazard assessments, the Select Agent regulations, the Biosafety Manual and operations manuals. A risk assessment for the maximum containment laboratory had been reviewed and approved by the Select Agent programme.

23. Job hazard analysis information was available and included information on the assessment of biological risk. A new tool is being developed (eRAMP). The WHO team recommended that this opportunity be taken to further develop the approach and ensure all hazards associated with biological agents are identified, assessed and managed, including the tracking and closing out of associated actions.

24. For risk control, incidents are reported through the Worker Incident Management System, for which performance metrics have been defined: record within two days and close case within five days.

25. The WHO team acknowledged the value of person-to-person communication within small teams such as the variola virus research group and of the trust established between its members for smooth work.

26. To manage security of contractors and suppliers entering areas designated by the Select Agent legislation, the federal government provided clear instructions for screening (by the Federal Bureau of Investigation) and the parameters were defined in the Statement of Work. The Statement of Work contains performance measures. Competitive bidding is the norm but there are mechanisms to justify single-source contracting when necessary or appropriate. Scientific support contractors needing to enter the BSL-4 facilities are approved and vetted in the same way as scientists and technicians, but with no access if the laboratories were operating in containment conditions.

27. The WHO team recommended that work continue on a comprehensive microbiological risk assessment for the variola virus research programme. CDC staff provided some examples of risk assessment, but the WHO team considered that the process could be carried out more systematically and better documented. It is also recommended that the need for standardized approaches be reviewed. This should include defining the entire scope of the activity to be addressed, together with training needs, tools and approaches in order to ensure that hazards and associated risks are effectively identified and any resulting actions are satisfactorily completed. Examples of areas that would benefit from a more formal risk assessment include the use of dunk tanks, working-alone policies and the effluent treatment system.

Pathogen and toxin inventory and information

28. Beginning in 2003, the variola virus research programme has established an electronic inventory database and associated systems for identification, accounting and information tracking of all materials containing live virus. The database is reconciled weekly, and a complete physical inventory check is performed at least annually.

29. The variola virus research inventory programme not only meets but exceeds all the requirements of Select Agent legislation. Although select agents are defined as infected material with documented viable virus, research specimens (such as tissues from infected animals) are also included in the inventory regardless of the fact that they are only assumed to contain infectious material. Inventory records are updated for such specimens upon verification of virus viability to reflect the presence of a select agent. The inventory stored in the electronic database is secured by three levels of protection. Physical reconciliation is done regularly, always in the presence of responsible individuals. CDC's training material identifies the process for logging materials that all users must follow. The WHO team was satisfied with the secure storage of material and archival stocks and its comprehensive tracking facility.

30. Efforts are being made to limit the amount of material being stored. CDC staff stated that when a research protocol ends, all samples are destroyed, and that single-use aliquot portions should increasingly be used.

31. The WHO team commended CDC for keeping all stocks of purified non-infectious variola virus DNA in highly secure environments. Access is restricted to a limited number of authorized personnel. As a further security measure the team recommended that virus genomic DNA should be diluted to a concentration suitable for polymerase chain reaction (or other diagnostic) tests and only these diluted genomic DNAs be stored in the working refrigerator/freezer.

General safety

32. A risk assessment exists for the original BSL-4 laboratory, job hazard analysis samples were provided, including those for animal work, but the inspection team had additional questions as to how these were used for specific aspects of variola virus work. A useful source of information for providing input to a risk assessment is a *job hazard analysi*s or *workplace hazard analysis*, a document that dissects the steps of a procedure or process and allows the user (a) to identify potential safety or health hazards, (b) to substitute or make changes to mitigate a potential risk or risks, such as introduction of engineering controls, and (c) to recommend additional training for the worker. The WHO team recommended that CDC consider documenting the process for conducting a risk assessment and subsequently managing the identified risks.

33. Currently, CDC does not mandate a two-person rule for individuals working in maximum containment. Two persons are recommended, in guidance within the operations manual, for work where actual handling of animals is undertaken. A policy instituting a two-person rule may serve as an adjunct to safety regarding the potential of a medical emergency. A second person within the maximum containment laboratory may be able to provide life-saving medical assistance and would be able to summon medical responders more rapidly than a person outside of the maximum containment laboratory. Concern was expressed about access to viruses by one person in the laboratory and it was recommended that working alone should be strongly discouraged. Recognizing the significant concerns expressed by various parties, the WHO team recommended that CDC should consider re-evaluating its rule in the light of WHO guidance recommending that the two-person rule should apply, and when conducting research with animals the two-person rule must apply (Reference: the World Health Organization *Laboratory Biosafety Manual*, 3rd edition).

Personnel and competency

34. The scientific programme defines its fixed-term staffing, including guest researchers from USAMRIID who are full-time equivalents registered as visiting scientists and work under CDC's rules. CDC policy has shifted to requiring anybody who needs to staff the containment facility to be a full-time equivalent member of the institution; however, trainees, such as post-doctoral fellows are granted time-limited access after achieving all required training certificates/authorizations. Visitors need appropriate clearance, and need to be US citizens. The requirement for immunization against smallpox will be indicated in a post description.

35. Considerable work has gone into training. On recruitment, all staff undergo basic training, which includes introduction to safety and security policies, and other rules and regulations, including information technology (IT) practices. Subsequent training in scientific programmes covers the requirements of the Select Agent legislation and guidelines specific to laboratories and pathogens as well as animal use. Users of BSL-4 labs are required to complete 50-100 hours of mentored extended training and demonstrate competency/proficiency before independent work is permitted. Satisfactory completion of training is signed off, and continued competence is checked at the annual performance review. Staff can also access an individual development plan. Such plans and training records, but not those for laboratory-specific training, are collected and stored. Select Agent training is recorded separately. The WHO team recommended that additional training about life-support measures in first-aid training should be given to CDC staff conducting work with live variola virus.

36. CDC underlined the low turnover rates of staff. The tight-knit nature of the variola virus research team makes for good communication. Levels of trust are high, and shared experience means that several members of the staff could step into leadership positions. Nevertheless, CDC staff are aware of the need for vigilance, especially about the behaviour of stressed or fragile individuals and have measures in place for counselling and, if necessary, removal of access rights (including IT services).

37. Good practice was described in the selection, training and competency assessment of scientific personnel. CDC's information technology personnel designated as having significant security responsibilities (i.e., those serving as administrators or granted elevated privilege (among other categorizations)) are required by regulations of the US Office of Personnel Management and policies of the Department of Health and Human Services and CDC itself to be vetted at public trust clearance or higher level. In addition, they are required to complete specific role-based training related to those responsibilities. This is tracked in the CDC Learning Management System and audited annually by the Office of the Inspector General.

Good microbiological technique

38. The WHO team endorsed the recommended policy that CDC staff should take steps to keep viral stocks to the minimum and encouraged the practice of working with one aliquot portion which is destroyed after use.