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Working Paper submitted by Australia

Trial Inspection of a Biological Production Facility

Introduction

At the Ad hoc Group session in November/December 1995, there was considerable debate on the potential utility of non-challenge (or routine) visits or inspections as an element of on-site measures to strengthen the BWC. At that time it was suggested that such visits could reinforce efforts to monitor activities relevant to compliance with the BWC, for example to provide assurances that the declarations were accurate. It was also suggested that such visits or inspections could have an information role, for example to convey information to a State Party relevant to Article X or Article V.

In June 1996 Australia undertook a trial inspection of a biotechnology company to develop and evaluate the utility of a relatively unintrusive inspection based on information provided by the company in a model declaration. The inspection was categorized as a trial routine inspection.

Objectives of the inspection

The objectives of the trial inspection were to:

- investigate the feasibility of verifying a declaration through a routine inspection;
- assess whether an inspection of this sort could have a deterrent function; and
- assess the impact of a routine inspection on the activities of a commercial facility, given the legitimate concerns which have been expressed about the impact of on-site inspection activity on industry. In particular, assessments were made of the extent to which activities at the facility would be interrupted or commercially sensitive information compromised. The views of the company management were also sought in this regard.

Conduct of the inspection

Declaration

In preparation for the inspection, the inspection team forwarded a questionnaire to the company, which formed a “model declaration” for the purposes of the inspection. The content of the questionnaire reflected suggestions which have been advanced during VEREX and in the discussions so far in the Ad hoc Group. The questionnaire sought details of the company’s activities under the following headings:

- Defense Ministry bio-defense program
- High containment facilities
- Aerobiology
- Work with microorganisms or toxins
- Genetic manipulation
- Production microbiology

Briefing by company staff

Upon arrival at the site, the inspection team was briefed by the site operations manager on the history of the company and on the general outline of its current activities. This included details of the company structure and the professional disciplines of the employees.

Working from a site plan, the manager of process development provided a technical description of the company’s activities, the production materials used, including microorganisms, the finished products and a general description of the manufacturing process. He noted in particular the activities conducted in each of the buildings on the site. The inspection team also reviewed the company’s declaration in the presence of both company officials. In summary, the inspection team was told that:

- the site covered an area of approximately 2.4 hectares;
- approximately 130 staff were employed at the site;
- the company currently produced an animal vaccine and planned to commence manufacture of a human therapeutic product in the near future;
- the facility contained several areas of BL2 containment including two production units, one of which could readily be converted to BL3 standards;
- the company did not work with any of the agents listed in the current FOC lists of human, animal and plant pathogens (BWC/AD HOC GROUP/29);
- no aerosolisation work was undertaken;
- genetic manipulation was undertaken, but not to enhance the pathogenicity of microorganisms;

- the company had no association with any government biodefence program.

Development of the inspection plan

Making use of the site plan and the information provided by the company officials during the pre-inspection briefing, the inspection team developed an inspection plan, in consultation with the company technical manager and production manager. The development of the plan took 15-20 minutes. It was agreed that the inspection plan would be flexible - that the inspection team would confine itself to the negative proof approach and would be no more intrusive than necessary.

The inspection plan was based on the list of specific on-site measures discussed in the FOC paper on On-Site Measures (December 1995).

(a) Visual observation/identification of key equipment

The company agreed that the inspection team could conduct a “walk through - talk through” inspection of the various parts of the plant site to obtain an overall visual impression of the types of activities being conducted, and to identify the types of key equipment being used.

However, the company expressed concern about some sensitive technological information related to production or processing (e.g. non-patentable “knowhow”) which the company would not want to share with the inspection team. It was agreed that in such cases, the application of managed access procedures, such as shrouding particular items (e.g. control panel information, or parts of intermediate processing equipment) would be possible to avoid loss of such information, while still allowing the inspection team to see sufficient of the process to be able to conclude that the activity was consistent with the declaration.

The company specified that for confidentiality reasons it would not allow photographs to be taken during the conduct of the inspection.

(b) Interviewing

The company indicated that in the course of the “walk through - talk through” inspection it would allow the inspection team to interview any of its staff. However, all interviews would need to take place in the presence of a member of the company’s senior staff as company management would need to provide guidance to an inspection team on whether the individual staff member being interviewed had the expertise/responsibility to enable accurate information to be provided in the areas which might be sought by the inspection team.

(c) Sampling and identification

The company officials expressed reluctance about sampling, but recognized that in some circumstances, sampling and analysis could more readily demonstrate compliance or clarify an ambiguity than other more intrusive inspection procedures, and hence reduce the duration of an inspection.

The company indicated that it would not object to samples being taken and analyzed as part of a BWC inspection provided that:

- The sampling was performed by a company official (in the presence of inspectors) from a standard sampling point, in a manner that would not disrupt any aspect of the production process.
- Any sample would be analyzed on site using a rapid screening method to check for the presence/absence of relevant organisms (or related bio-marker compounds), but would not attempt a complete identification of the components of a sample).

The company agreed that if a request for a particular sample was impractical, it would attempt to provide an alternative sample (e.g. from downstream production, filters or waste effluent area) which would satisfy the request of the inspection team.

The company emphasized that for confidentiality reasons, no samples would be permitted to be taken off-site.

It was agreed that no samples would be taken during this trial inspection.

(d) Auditing

The company agreed to allow access to all purchasing and financial records, including records of purchases of microorganisms. (Under Australian Government quarantine regulations, managed by the Australian Quarantine Inspection Service (AQIS), all purchases or other transfers of microorganisms in Australia are registered.)

It was also prepared to allow access to the monthly production records for the declared activity (production of animal vaccine) and more detailed records on a random selective basis (in which the inspection team was able to request to see a fixed percentage of the relevant parts of a number of records of its choice).

(e) Medical examination

It was agreed that medical examination of company officials would not normally be part of a routine inspection, although vaccination records may be useful to clarify an ambiguity. The company volunteered that conditional upon the agreement of the individual staff selected, it would have no objection to blood samples being requested from any of its employees.

Details of the inspection

1. Animal vaccine production plant

The inspection team walked from the reception area to the Animal Vaccine Production Plant and observed the operations within this plant.

Result - The Animal Vaccine Production Plant was observed to be a modern production area, operating under BL2 conditions, with fermenter and purification systems consistent with the types and quantity of animal vaccine noted in the declaration.

2. Research and development laboratories

The inspection team walked through all of the company's research laboratories. These laboratories contained a number of Biosafety Level 2 Cabinets, small fermenters (up to 10 litre capacity), and constant temperature rooms. Because of the capability of such research and development fermenters to produce militarily significant quantities of biological agents, the company was prepared to allow access to appropriate records (e.g. daily production records) on a random selective access basis to provide assurance that the fermenters were being used for the activities outlined by the company during the pre-inspection briefing, and not for any activities in violation of the BWC.

Result - The inspection team concluded the research laboratories were not configured for the handling of highly pathogenic organisms or for large-scale biological production. None of the employees were wearing the types of protective clothing which would suggest the presence of pathogenic organisms.

3. BL2 production facility - not in production

The inspection team walked through the newly constructed production facility, including the services area above the production area of the facility.

Result - The production facility was observed to be a modern production area, with the capacity to operate at negative pressure and to handle pathogenic organisms under BL3 conditions. At this stage the facility was not in use.

4. Auditing

A random selective access approach to auditing was developed to provide confidence in the accuracy of the information provided in the questionnaire relating to production of the animal vaccine.

Initially the inspection team was shown information on production quantities for the animal vaccine on a month-by-month basis. The inspection team was then able to select to see more detailed information from two to three months of the year (for example, perhaps where production was lower than average). The company provided more detailed production figures for these months, masking as appropriate any company confidential information. For time periods within the selected months where there was lower production, the inspection team was then able to request daily plant production records, which indicated the reason for the lower production (for example, equipment down for maintenance, off-batch of product).

Result - The inspection team was able to gain assurance that any lower than expected monthly production figures were not indicative of diversion of material (or use of the equipment) for undeclared purposes in violation of the BWC, and that the records inspected were consistent

with the information provided by the company in the questionnaire. The company was comfortable with this random selective access approach in that it was not overly time-consuming and did not risk confidential proprietary information.

5. Storage areas and outbuildings

The inspection team walked through the workshop, solvent store and other storage buildings associated with the facility.

Result - None of the workers at these sites had protective clothing to suggest the presence of pathogenic organisms. The activities being undertaken in the workshop were consistent with the company descriptions of its functions. The level of security at both the workshop and the various storage buildings was consistent with normal practice at a commercial biotechnology research/production facility and with the company indication that no high-risk agents were present.

6. First aid area/sick bay

One member of the inspection team was shown the company's first aid area.

Result - The sick bay was observed to be a small room containing a bed and a small medicine cabinet. There were no medicines or therapies relating to the treatment of exposure to, or protection against, pathogenic organisms such as large quantities of antibiotics, antidotes to toxins, vaccines related to listed agents or isolation areas for treating infected employees.

Conclusions

The inspection team concluded that the company was operating a legitimate commercial facility and observed no evidence of any BW-related activity. All of the equipment and activities observed during the inspection were consistent with the details provided by the company in the questionnaire and with the additional information received from the company during the initial briefing. Using a random selective access approach, the inspection team was also able to check the production information provided by the company in the questionnaire. It was thus concluded that an inspection of this type would provide a high level of assurance in the accuracy of information provided by the company in the questionnaire and in the company's compliance with the BWC.

The company was satisfied that the inspection team did not interfere with either the research or production activities of the company. It was also satisfied that the inspection team had taken appropriate measures to protect commercially valuable information and data and did not foresee any specific difficulties with receiving inspections based on the principles which had been followed in this trial. The company management noted that the company received more intrusive inspections under the Australian Therapeutic Goods Administration licensing procedures and is expecting to be subject to intrusive inspections under the U.S. Food and Drug Administration inspection process in connection with the manufacture of a human therapeutic product.

The inspection team noted that for an inspection to be effective, attention would need to be given to the professional expertise of the inspection team. In addition to microbiologists, biochemists or physicians it was clear that because of the importance of high containment in the handling of pathogenic organisms an inspection team should include an engineer familiar with the construction and operation of biotechnology production facilities. Given also the importance of records auditing, the inspection team should also include a member with experience in records management. It was concluded that provided that the inspection team possessed this range of expertise, a routine inspection at a reasonably sized commercial biotechnology production facility could be completed within one day.

The inspection team was satisfied that using this approach a routine inspection could be achieved in a manner which would not disrupt production in a commercial biotechnology facility, and by the application of appropriate managed access procedures (including random selective access of production records) would not jeopardize confidential information.

Based on the experience of this trial inspection, we consider that a system of routine inspections on certain types of biotechnology facilities would significantly deter violations by imposing a substantial risk of discovery and, at the same time, would provide mechanisms for demonstrating compliance that would enhance confidence that other States Parties were in compliance with the BWC. Australia is planning to conduct additional trial inspections to further develop and refine procedures for BWC verification of commercial biotechnology facilities.
