World Health Organization

Containment verification of large-scale polio vaccine production and quality control facilities following the interruption of endemic poliomyelitis transmission

Discussion group on global containment strategies

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This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization.

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Abbreviations and acronyms

AFP	Acute Flaccid Paralysis
BSL	Biosafety Level
BSL-3/polio	Poliovirus-specific Biosafety Level 3 containment
cVDPV	Circulating Vaccine Derived Polio Virus
ECBS	WHO Expert Committee on Biological Standardisation
GAP	Global Action Plan
GCC	Global Certification Commission
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
iVDVP	Immunodeficiency Vaccine Derived Polio Virus
IPV	Inactivated Polio Vaccine
mOPV	Monovalent Oral Polio Vaccine
NRA	National Regulatory Authority
OPV	Oral Polio Vaccine
PEI	Polio Eradication Initiative
sIPV	Sabin Inactivated Polio Vaccine
wpvIPV	Wild poliovirus Inactivated Polio Vaccine
VAPP	Vaccine Associated Paralytic Poliomyelitis

Summary of conclusions

1. **Commissioning of BSL-3/polio containment in large-scale polio vaccine facilities.** Given the importance of implementing a uniform and adequate containment of poliovirus to protect the benefits of poliomyelitis eradication, particularly in the case of the large-scale production of wild-type poliovirus, a formal verification of implementation (commissioning) of BSL-3/polio containment within all IPV manufacturing and quality control facilities should be conducted.

2. **Qualifications of commissioning authorities.** Member States with IPV production and quality control facilities must themselves determine which national authorities need to be involved in commissioning of BSL-3/polio containment measures within their borders. However, given the global nature of the polio eradication initiative, to insure that adequate, uniform, and equitable standards for biosafety and poliovirus containment are met in all facilities, sufficiently qualified technical experts in biosafety and biocontainment with full knowledge of the requirements and implementation of BSL-3/polio measures across multiple locations should be included as an integral part of national commissioning and re-commissioning assessment teams. Appropriately trained and qualified technical experts may be provided by WHO for this purpose.

3. **Commissioning procedures.** To insure a uniform and equitable implementation of the BSL-3 containment guidelines across all sites, all nations, even those with recognized experience and expertise in biosafety and containment, should adopt identical and equal commissioning and re-commissioning procedures. WHO should provide a detailed description of the criteria and procedures to be used for BSL-3/polio commissioning. Commissioning should consist of an initial verification assessment of the conformity with BSL-3/polio containment. Both a review of documentation describing the implementation of containment measures as well as an on-site assessment by an appropriately qualified commissioning team are considered necessary. To ensure adequate maintenance of containment after commissioning, routine re-evaluations of BSL-3/polio IPV facilities should be conducted at regularly intervals to monitor that the provisions of the guidelines are maintained at a satisfactory level. WHO should develop guidelines on how the scope and frequency of such routine assessments should be determined through a risk analysis approach.

4. **Legal status of commissioning.** In some Member States WHO BSL-3/polio containment guidelines may have legal status; in those where this is not the case, Member States should adopt the requirements into their legal structures. A mechanism should be established where BSL-3/polio requirements can be implemented even if conflicting legal requirements exist. A World Health Assembly resolution, binding on all Member States, would provide a valuable basis for insuring the global implementation of adequate containment measures.

5. **Harmonization of BSL-3/polio requirements with other regulations.** BSL-3/polio containment measures will add a new aspect to the quality of medicinal products produced from poliovirus, and their implementation must be viewed as a priority to be met along with other pre-existing requirements. Member States must develop a consensus approach on how to deal with potential conflicts that may exist between existing requirements and the BSL-3/polio requirements, with the aim that the BSL-3/polio requirements are implemented. WHO should facilitate this activity with national and regional authorities to the greatest extent possible through the establishment of uniform requirements for variations to existing establishment and product licenses. Member States should make every effort to ensure that such assessments are conducted as a collaborative effort between national and international interests, as well as minimizing the potential conflicts that might arise when other nations (e.g. importing countries) may wish to conduct independent assessments that might not be harmonized with the established requirements for commissioning.

6. **Facilities failing to implement BSL-3/polio containment measures.** It is recognized that some companies may not have the will or the resources to implement or maintain the BSL-3/polio containment at an appropriate level. However, it must be insured that all operating companies have implemented BSL-3/polio conditions at the point in time when the need arises. WHO should explore all possible political or legal mechanisms with the involved Member State for ensuring that such companies do not pose a threat of reintroducing poliomyelitis into an increasingly susceptible global population.

7. **Containment requirements for wild poliovirus when global immunity starts to decline.** BSL-3/polio containment of wild poliovirus will be sufficient while global immunization coverage remains high. There was no consensus on whether BSL-3/polio containment will be adequate to protect an increasingly susceptible population at the point when immunization coverage starts to decline. It may be that BSL-3/polio conditions provide sufficient safeguards to protect the global population, but it is also possible that given the large amounts of poliovirus produced and the degree to which high titer viral stocks must be handled, that even BSL-4 technologies may not provide adequate safeguards when large segments of the global population become serologically naive. The time frame for implementation of an appropriate system of containment will be dependent on the rise in susceptible populations regardless of cause. WHO should convene a group of biosafety experts to examine the biohazard risk level of poliovirus as a function of population immunity. Additional data could be collected (e.g. infection and shedding of virus by production and QC operators, or environmental sampling) to help conduct this risk assessment.

8. **Containment requirements for IPV produced from Sabin attenuated strains.** Currently Sabin strains used for the production of vaccines are manufactured under GMP (BSL-1) conditions. When Sabin strains are no longer administered as live virus vaccines and circulating freely in the environment, the containment level will have to be increased corresponding to the risks associated with VAPP and VDPV events resulting from an unintentional release into the environment at that time.

   WHO should co-ordinate the development of specific guidelines for the safe production and quality control of Sabin-IPV, defining both containment, quality assurance, and quality control testing appropriate to this product during the post-certification era. This development should include an on-site assessment of current Sabin virus production sites, including developing country manufacturing sites where biosafety experience and expertise may not be as accessible as in industrialized country settings.

9. **Containment requirements for new oral vaccines produced from Sabin strains.** When vaccine-derived Sabin strains are no longer freely circulating in the environment, the production and quality control of Sabin OPV must take place within appropriate containment facilities. The biohazard risk level for OPV viral production would likely be the same as for the live-virus production areas of Sabin-IPV; the containment zone would however need to be enlarged to include additional production and QC activities. WHO should co-ordinate the development of containment guidelines for the safe production and quality control of Sabin oral polio vaccines for the post-certification era, with primary emphasis on the construction and maintenance of global and / or national emergency response stockpiles. In the event that Sabin strains must be administered as a live-virus vaccine in an emergency response situation, the containment levels required for stockpile production and maintenance will no longer be applicable within the affected area, and mechanisms should be put in place to automatically reduce the biohazard risk level to that appropriate for the unrestricted use of OPV.

1. Background

1.1 Poliovirus containment requirements following the cessation of endemic poliomyelitis transmission

The WHO "Global Action Plan for Containment of Wild Polioviruses" (GAP) was formulated as a policy guideline for the containment of poliovirus in the post-certification era. In the GAP, it was recognized that special precautions will be needed for the commercial production of poliovirus needed for the two existing polio vaccines, inactivated polio vaccine (IPV) produced from wild strains, and oral polio vaccine (OPV) from attenuated strains. As long as these large-scale viral production facilities remain in operation, effective containment of the poliovirus produced in them must be implemented on a global scale; at the same time, these facilities must continue to conform to the strict regulatory requirements placed on medicinal products while meeting the global vaccine demand.

In the initial GAP published in 1999, containment levels were established as a function of global population immunity. Inactivated polio vaccine manufacturers producing polio vaccine from wild poliovirus strains (wpvIPV) were required to implement polio-specific Biosafety Level 3 containment conditions (BSL-3/polio) one year after the last occurring wild poliovirus transmission, when immunity due to silent infections of endemic poliovirus would no longer occur. At the point where immunization with OPV would decline and substantial populations of unprotected persons would arise, BSL-4 conditions were to be implemented. Attenuated (Sabin) poliovirus strains were to be contained in BSL-2 conditions and BSL-3 conditions at these two time points. In the revision of the GAP published in July 2003, the BSL-3/polio requirement for wild poliovirus remains in force albeit implementation will be delayed by one year; the remaining containment requirements were suspended pending further developments in immunization policy. Thus two essential activities must be carried out to insure that poliovirus containment is effective when the epidemiological need arises. First, a mechanism must be put in place that guarantees that effective containment is implemented uniformly and on a global scale; in this era of rapid transit of persons and materials, it would serve little purpose to implement them in one region while in another they are not. Second, it must be recognized that several years of intense effort will be needed to build and approve the new biosafety facilities required to produce vaccines for the post-certification immunization scenarios under consideration. The containment requirements for the existing poliovirus-based vaccines need to be established well in advance if future vaccine demand is be met without any breach in biosafety or biosecurity, and biosafety requirements for new polio vaccines need to be established as an intrinsic part of their development plan if they are to be implemented.

1.2 Determinants of global polio immunization policy following certification

The goal of the post-certification immunization strategy is to maintain polio-free status at the lowest possible cost in terms of disease and financial burden. This goal can be reached through the maintenance of an optimal immunization policy to protect populations once endemic transmission has been stopped, combined with continuing surveillance and emergency response capacities. Four major post-certification immunization policies remain under consideration: cessation of all polio immunization; continuation of OPV and IPV

policies as they exist today; cessation of OPV and switching to universal IPV coverage; or the development an ideal new polio vaccine with neither containment nor serious adverse event risks. The basic question that will drive the selection of future policy will be whether OPV is needed following certification; if the answer to that question is no (or if the risks associated with OPV use following certification are considered too high), then it must be considered whether a switch to universal immunization with IPV is necessary. Many open issues remain to be solved before a scientific recommendation will become available, and it is likely that the final decision will rest on a complex mixture of scientific, economic, and political factors. Under the current situation, these policy decisions could be brought to the World Health Assembly as an information item in 2004, and for initial debate as early as 2005.

1.3 Establishing polio vaccine quality standards for the post-certification era

With the cessation of wild poliovirus transmission and regional certification in the American, European, and Western Pacific Regions, increasing numbers of industrialized countries have discontinued routine immunization with OPV and have switched to wpvIPV use. This change has been driven largely by the occurrence of OPV-associated paralytic poliomyelitis (VAPP) and the development of IPV-containing multivalent vaccines with most of the antigens needed for routine childhood immunization. This trend is expected to continue in other countries. In contrast to smallpox eradication, where the elimination of the disease had little effect on the ability to produce *vaccinia* vaccines, a continued need for poliovirus-based vaccines during the post-certification era will mean there is a sustained risk of reintroduction from vaccine manufacturing facilities. In the unique situation where the inadvertent release of such strains might have disastrous public health consequences, adequate containment measures must from now on be viewed as an intrinsic part of the safe production and quality control of these vaccines.

1.4 BSL-3/polio containment guidelines for vaccine production from wild poliovirus strains

Specific BSL-3/polio containment guidelines for the production and quality control of IPV manufactured from wild polioviruses were adopted in February, 2003 by the WHO Expert Committee on Biological Standardization (ECBS). The WHO "Guidelines for the Safe Production and Quality Control of IPV Manufactured from Wild Polioviruses" take into account the specific needs of a large-scale facility producing this medicinal product. These guidelines were formulated through a procedure involving visits to all existing IPV manufacturing sites followed by a series of interactive consultations with representatives of the biosafety community, national regulatory authorities, and existing IPV manufacturers and companies considering the development of such products. The intent of the guidelines is that they must be adopted by all Member States according to the time lines identified; modifications to the content of the requirements should be made only if an equal or superior level of containment is guaranteed.

2. Existing requirements and oversight mechanisms for polio vaccine production

Vaccine producers are subjected to a number of existing governmental requirements, with simultaneous compliance to each a prerequisite for their license to operate. For companies that export vaccines, it may also currently be the case that different (and at times contradictory) requirements for each importing nation may also need to be met. It is within this complex network of existing governmental controls and legal requirements that BSL-3/polio containment measures must be introduced, raising questions on how priorities will be set, how potential conflicts between existing and new requirements can be resolved, and how the commercial interests involved in maintaining adequate vaccine supplies will respond.

2.1 Establishment and product licensing for medicinal products

The production of medicinal products must take place in an establishment which is licensed by the national government. Establishment licensure is dependent on whether the company complies with national Good Manufacturing Practices (GMP) for medicinal products for use in man. Importing countries may also require conformity to their own national GMP rules regardless of where the manufacturer is located, making the conformity to multiple regulatory systems within the same facility the norm rather than the exception. In all countries, GMP is focused on the protection of the end-user of the medicinal product and not on protection of the production worker or the environment. As a sterile biological product, IPV production and quality control fall under the most highly detailed and specific of GMP requirements. With the introduction of high-level biosafety technology and practices, centered on keeping contaminants within the production zone (where the medicinal product is being manufactured) rather than expelling them into the environment, a number of perceived or real inconsistencies may be noted in the course of GMP audits that will need to be resolved in a flexible, case-by-case approach as BSL-3/polio containment is implemented.

Each product must additionally have a marketing licence based on quality, potency, safety, and efficacy data prepared by the company and submitted to the National Regulatory Authority (NRA) for approval. A description of the facilities used in manufacturing and testing of the product is part of the submission. Significant changes to these descriptions normally require notification or prior approval (a “variation” to the product license), and in cases of significant changes to facilities or procedures, new product licensure may be required. The important regulatory decision when introducing containment requirements into IPV production will be whether these changes to the manufacturing or quality control processes, facilities, equipment, procedures, and specifications will change the product. With approximately one year required to obtain approvals following the submission of completed applications for a change, adequate time must be planned for these regulatory steps. The regulatory procedures and the scientific data needed to support the product variation might be coordinated by WHO to streamline this process.

2.2 Environmental protection, worker safety and health, and civil defence issues

Local regulations are in force so that the population and the environment are protected from the release of potentially pathogenic organisms, and various ministries or agencies at the local or national level may become involved with any increase in the biosafety status of a vaccine production facility. In some countries, the authority for the protection of the environment may be limited to specific organisms, e.g. to those with genetic modifications, or may be delegated to local government agencies more concerned with the routine problems connected with waste management. The protection of workers in facilities handling pathogenic organisms may also be regulated, although significant differences exist between countries on what constitutes a safe environment, and the extent to which these regulations are applicable to the manufacture of medicinal products. Transport, import, and export of biohazards materials fall under national and international regulations, often with multiple agencies assigned to control movements of these materials in national and international commerce. The biosecurity of select agents is becoming increasingly prioritised in a number of countries and often involves national military and defence interests. It may thus be that conflicting legal authority exists between ministries or agencies responsible for these diverse areas of biohazards oversight, and a high degree of coordination will be needed to secure the collaboration of all involved public health partners in implementing poliovirus containment measures.

2.3 Commercial factors affecting vaccine availability

Vaccine production must comply with all applicable local, national, and international requirements, but additionally must be industrially feasible and economically sound. At least five years will be needed from the time a decision is made to introduce a change until regulatory approvals are obtained and production of the new product can start. In the case where the change affects an antigen present in combination vaccine preparations, such as in IPV-containing multivalent vaccines, the magnitude of these complexities increases proportionally. Vaccine producers are fully aware that polio vaccines will remain an essential tool for the public health, and are committed to supply these vaccines to a world soon to become polio-free. It must however be recognized that if future immunization policies are to be realistic, vaccine demand must be significantly better planned than has been the case in the past, and technical changes must be announced sufficiently in advance of the time when they are to be implemented.

2.4 Commissioning of high-level containment facilities

Biosafety commissioning of high-level containment facilities is designed to provide assurance that the facility is safe to operate before it is allowed to do so. Commissioning is based on performance verification and testing, focusing on the physical containment facility and personnel protection. In addition to biosafety containment standards, numerous other standards need to be applied to such facilities, including building codes, fire codes, health and safety standards, specialized equipment standards, and so on. Commissioning should take place upon completion of construction, upon major renovation, and routinely thereafter. Biosafety commissioning should be carried out by highly qualified and trained personnel, specialized in testing air-handling systems and performing biological indicator tests, pressure vessel tests, alarm systems, security systems, and safety procedures.

3. Verification of BSL-3/polio containment within vaccine production and quality control facilities

3.1 Verification of BSL-3/polio containment

Following the cessation of endemic wild poliovirus transmission, an increased biosafety risk will be associated with polio vaccine production and quality control sites due to the scale and complexity of the facilities, the very large quantities of poliovirus produced, and the need to repetitively sample and test high-titered viral stocks. Combined with the need to comply with a range of competing regulations, some of which may not be compatible with traditional biocontainment concepts, an independent and impartial assessment of the implementation of BSL-3/polio containment would appear to be essential if global compliance is to be assured. The possibility of new IPV manufacturing sites initiating production in countries where there is little available expertise or experience in the design, procedures, equipment, and maintenance of high-level containment facilities would similarly argue for the necessity to conduct commissioning activities based on a uniform set of criteria on a global scale. It is recognized that the vaccine production company will retain the primary responsibility for the day-to-day operation of the containment facility, but in all cases both the manufacturer and the oversight authorities would benefit from a formal assessment of the degree to which adequate containment has been implemented at the point in time when the specified containment level is required.

Conclusions:

- Given the importance of implementing a uniform and adequate containment of poliovirus in protecting the benefits of poliomyelitis eradication, particularly in the case of the large-scale production of wild-type poliovirus, there is full consensus that a formal verification of implementation (commissioning) of the BSL-3/polio containment guidelines within IPV manufacturing and quality control facilities should be conducted in all sites.

- Certain companies or countries with an established record in implementing containment technology may feel that an exception should be made in their case, and that a self-assessment or abbreviated procedure would be adequate. This may well be true, but in all cases without exception a full and independent commissioning of these critical facilities should be conducted.

3.2 Expertise and experience required for commissioning high-level containment facilities producing medicinal products

With the inclusion of BSL-3/polio containment provisions into IPV quality specifications, NRAs will be faced with the difficult task of insuring the continued safety and efficacy of a

medicinal product while simultaneously managing the risks of reintroducing poliomyelitis on a local, national, or global scale. Environmental and worker protection authorities are responsible for certain environmental aspects of BSL-3/polio, but may not be fully cognizant of the requirements for manufacturing medicinal products, or, as in some countries, their mandate may extend primarily to special conditions such as the control of genetically modified organisms. This complex situation where heavy demands will be placed on highly-specialized authorities could lead to situations where the BSL-3/polio containment facilities are required to follow GMP rules exclusively, to the detriment of the effective containment, or to follow environmental or worker protection rules exclusively, to the detriment of GMP and medicinal product requirements. National controls could also be overly stringent compared to the global average, resulting in an excessive level of restrictions placed on national manufacturers, or less demanding compared to the global average, resulting in facilities that pose a greater risk of poliovirus escape than the global norm but nevertheless enjoy a commercial advantage over companies that are fully in compliance.

The necessity to implement containment measures globally and without exception would therefore argue for the inclusion of an international component into what is traditionally a national responsibility. The technical advice of biosafety experts of international standing, familiar with poliovirus and the BSL-3/polio containment requirements and experienced in the implementation of these containment requirements across several facilities, would appear to provide an essential element to the commissioning process.

Conclusions:

- While the assurance of vaccine quality will remain a national responsibility, the biosafety and biocontainment aspects of large-scale poliovirus vaccine manufacturing and quality control facilities following interruption of endemic transmission of poliovirus will become an international concern. WHO should take a lead in ensuring that containment measures are implemented uniformly, equitably, and without exception.

- Member States with IPV production and quality control facilities must themselves determine which of their national authorities should be involved in the commissioning and re-commissioning of BSL-3/polio containment measures within their borders. They must establish a collaborative relationship between these responsible agencies so that conflicts are expeditiously resolved and the priority of BSL-3/polio containment is maintained.

- While GMP assessments remain necessary to protect the end-user of the vaccine, GMP inspectors, unless they have developed a significant amount of expertise through specialized experience and training, should not be viewed as having the appropriate qualifications to conduct BSL-3/polio containment assessments.

- WHO should provide appropriately trained and qualified technical experts in the field of BSL-3/polio containment to assist and advise Member States in commissioning IPV production and quality control facilities. These experts should serve as part of the assessment team during commissioning, although the authority for commissioning must be retained by the Member State

- Conflicts may arise between the diverse requirements established by multiple national and international public health partners. A flexible solution based on consensus rather

than compromise should be sought so that BSL-3/polio containment can be fully implemented while respecting the mandates of existing oversight authorities.

3.3 The legal basis for commissioning

Commissioning activities will involve the entry of independent assessors into the company and require access to all information necessary to conduct a full and thorough audit. The assessment team may require physical evidence or photographs of their findings. Should deficiencies be found, the commissioning team may require that they are remedied. Commissioning activities that are based solely on the voluntary compliance of the company are unlikely to be successful, especially when the company feels that the recommendations are unwarranted. Conversely, should inconsistencies arise between the containment requirements and other existing national requirements, such as GMP, GLP, product licensing laws, or environmental or worker protection laws, the company should be protected from penalties arising from their implementation of the BSL-3/polio containment guidelines.

In some countries, WHO guidelines are transcribed into national requirements and given the force of law; in others, they are viewed as recommendations only, with separate national laws applicable to vaccine manufacturing. Each Member State must take the appropriate steps to ensure that in this exceptional case, a legal basis for requiring BSL-3/polio containment in vaccine manufacturers is in place at the time of commissioning, and that governmental authorities are given sufficient leeway to make modifications to existing provisions where containment constrains may take precedence over routine requirements.

Conclusions:

- Member States have the authority and legal basis for ensuring the protection of end-users of medicinal products, the environment, worker safety and health, and civil defence. Internationally harmonized requirements for the biocontainment of polio vaccine production and testing facilities should be integrated within this pre-existing legal framework so as to be available at the time of commissioning.

- A World Health Assembly resolution, binding on all Member States, would provide a valuable basis for insuring the global implementation of adequate containment measures.

3.4 Commissioning methods and procedures

Commissioning activities should be conducted before the facility is ready to start its operation at BSL-3/polio containment. The commissioning assessment should involve a detailed examination of the planning, construction, functioning, and validation of the facility, as well as applicable operating procedures and records. An on-site assessment will in all cases be necessary. When in the judgement of the commissioning team the facility meets the established standards, it can be certified as being in conformity and authorized to commence activities. Every effort should be made so that companies are not confronted by sequential assessments from multiple countries, each demanding conformity to their national requirements which may or may not be harmonized with WHO containment guidelines. Novel mechanisms, such as the identification of harmonized regulatory requirements, or arranging a joint or mutually recognized assessment satisfactory to all interested parties could be considered.

Conclusions:

- To insure a uniform and equitable implementation of the BSL-3 containment guidelines across all sites, all nations should adopt identical and equivalent commissioning and re-commissioning procedures. WHO should provide a detailed description of the criteria and procedures to be used for BSL-3/polio commissioning.

- Commissioning should include an initial assessment of the conformity with BSL-3/polio containment when the site intends to enact it. Both a review of documentation describing the implementation of containment measures as well as an on-site assessment by an appropriately qualified team are considered necessary.

- Member States must develop a consensus approach on how to deal with potential conflicts that may occur between existing requirements and biosafety measures so that the BSL-3/polio requirements are adequately implemented and the risks of reintroduction of poliomyelitis are reduced to an acceptable level. WHO should facilitate this activity with national and regional authorities to the greatest extent possible.

3.5 Commissioning results

The identity of the authority that confirms that a facility is in compliance with BSL-3/polio containment must be carefully considered. Even with a joint assessment team composed of national and international interests, if international experts are allowed to dominate the assessment this could lead to an infringement on national oversight mechanisms or a lack of incentive on the part of the Member State to actively participate in the commissioning process. With assessments conducted predominantly through national interests, the international BSL-3/polio expertise may not be weighted to the extent required. A joint reporting system should be worked out whereby both national and international conclusions can be independently communicated. In this situation, both parties would have to be in agreement that the facility adequately conforms to BSL-3/polio containment conditions for it to be commissioned and allowed to operate. In the case where either party concludes that BSL-3/polio conditions are not in place, the operations of the facility should be stopped until corrective actions can be taken and verified. In the case where the facility meets BSL-3/polio containment but fails to conform to other national regulations (e.g. national GMP standards), the Member State can meet its international certification requirements while the national authorities conduct their independent compliance activities. Various methods can be utilized to signal the agreement between national and international authorities that BSL-3/polio containment is in place. If the Member State has adopted BSL-3/polio containment measures into their legal requirements, a certificate of compliance could be issued by the national government. This would indicate the commitment of the national government to introduce and maintain BSL-3/polio containment conditions within their national borders. In most cases, this would be the NRA in the course of a GMP assessment triggered by the implementation of BSL-3/polio containment measures. An independent report considering the degree of implementation of BSL-3/polio containment could be submitted by the international BSL-3/polio observer directly to the Global Commission for the Certification of the Eradication of Poliomyelitis.

In the case where a company cannot or will not implement adequate compliance to the BSL-3/polio guidelines, live poliovirus production and quality control activities should be fully stopped and the live-virus facilities decontaminated. When the company has signaled that it

has the intention to meet all requirements, commissioning assessments can be resumed. In the case where there is founded suspicion that a company is continuing with wild poliovirus production and quality control testing without having successfully implemented BSL-3/polio containment measures, regardless of the support or lack of support of the NRA, WHO should directly engage the political leadership of the country at the appropriate level to identify the public health dangers involved and assist the leadership in implementing a decontamination and inactivation of the facility on an emergency basis.

Conclusions:

- For the site to be commissioned, both the competent authorities within the Member State and the international BSL-3/polio observer should be in agreement on whether BSL-3/polio containment has been adequately implemented.

- A responsible authority of the Member State designated for that purpose should certify that BSL-3/polio containment of IPV production and testing facilities with their borders has been implemented. The international BSL-3/polio observer should independently state his or her conclusion that the site meets BSL-3/polio containment requirements.

- A company may have deficiencies in their implementation of BSL-3/polio containment at the time of assessment, but the assessment team may nevertheless conclude that the facility is commissioned provided that it takes corrective actions within an agreed-upon time frame. The legal authority of the Member State must be called upon to insure that such corrective actions are taken.

- If companies do not have the will or the resources to implement or maintain the BSL-3/polio guidelines at an appropriate level, a full cessation of poliovirus production should be mandated until such time as corrective measures have been implemented and verified.

- If any one Member State fails to adequately implement BSL-3/polio containment at the correct point in time, this should be viewed as an urgent public health emergency requiring immediate action. Sufficient political pressures should be brought to bear to effect an immediate cessation of activities posing a risk of reintroducing poliomyelitis.

3.6 Containment maintenance

Routine re-assessments are required for high-level containment facilities to ensure that their certified standards are being maintained; in the case where performance has significantly deteriorated to the point where critical or major deficiencies in its operation are detectable, the facility should be decommissioned until such point that its adequate functioning can be resumed. With the multidisciplinary nature of the oversight mechanisms in place, there should be a close cooperation between company, NRA, and international authorities to insure that no changes are made to the commissioned containment system without prior approval.

Conclusions:

- Manufacturers should qualify or validate the performance of BSL-3/polio containment within their facility on a regular basis. In most cases, a validation of critical systems should be conducted at least annually.

- Re-commissioning of BSL-3/polio sites should be conducted on a regular basis by a team of national and international experts sufficiently skilled to perform this task. The periodicity of such assessments should be established by an assessment of the risks involved, and guidance on how this can be determined should be circulated by WHO to insure a common approach. Initial re-assessments should be conducted two years after the initial commissioning, but this period may be extended to no longer than every five years.

- Major changes in containment systems, facilities, equipment, and management structures may warrant a re-commissioning assessment.

4. Future containment requirements for IPV produced from wild poliovirus

4.1 Biohazard risk level as a function of global population immunity

Micro-organisms are assigned to one of four biohazard risk levels (1-4) through an assessment of their pathogenicity, transmissibility, and the availability of preventive measures or treatment. The biosafety measures appropriate for the containment of escalating biohazard risk levels will involve a combination of engineering, administrative, and emergency controls that together can provide adequate containment under even the most challenging situations. The unintentional release of poliovirus from a wpv-IPV facility could however occur through contaminated liquid, solid, or gaseous effluents, through breaks in the containment barriers through technical accidents, acts of nature, biosecurity failures, or from contaminated operators or their clothing. It is increasingly difficult to assign a probability to such events; many incidents have gone unnoticed with the universal immunization of workers and their surrounding populations, and increasingly due to liability concerns laboratory accidents remain unreported and undocumented. However, it is clear that the consequences of seeding poliovirus into the environment will become more severe as populations of unimmunized persons develop in the absence of circulating endemic wild poliovirus and a decline in vaccination. While an increased biocontainment level can provide additional safeguards against poliomyelitis reintroduction, it is also inextricably associated with increased operating costs and decreased vaccine production capacity that can have a profound impact on future immunization policies. These restrictions must be carefully considered well in advance of any change in global immune status.

4.2 Long-term risks associated with wild-virus IPV production and quality control facilities

There is complete consensus that at the present time, when high levels of immunity are maintained by vaccination, BSL-3/polio containment is adequate for large-scale wpv-IPV production and quality control facilities. However, many open questions remain concerning the adequacy of this technology when susceptible populations arise. Immunization of workers within the live-virus zones do not provide life-long mucosal immunity, and even then, no current vaccine (IPV or OPV) is thought to completely eliminate silent infections and shedding. Poliovirus can indeed "walk out" of a facility through incompletely decontaminated clothing or wastes or silent infections of immunized personnel, and these risks increase proportionally if higher capacities of IPV production will be needed. From one perspective, the current BSL-3/polio requirements are very comprehensive, and relatively few additions would be required to achieve adequate containment when population immunity would start to decline. Even if measures must be added to bring them to a BSL-4 containment level, new advances in self-contained suits for production personnel combined with classical BSL-4 laboratories for quality control might well be feasible within the existing facilities, although clearly many manual operations would have to be replaced

with automated systems. From another perspective, however, the level of security must be raised as high as possible due to the very large amounts of poliovirus being produced and the magnitude of the public health emergency that could be triggered from even a single release into a susceptible population; even full BSL-4 containment has its inherent technical risks, and only a full cessation of the large-scale production of wild poliovirus strains will supply the necessary level of security for the post-immunization era.

4.3 Development of future containment facilities for wild-poliovirus IPV

The experience of some if not most wpv-IPV manufacturers has been that extensive renovations are necessary to increase a (BSL-1) GMP production facility to BSL-3/polio containment facilities. In some cases, new buildings for production and quality control have been necessary to meet the needs of negative pressure cascades and full waste treatment of gasses, water, and solids. Raising the biocontainment level from BSL-3/polio to a higher level will involve increased costs and decreased production capacity. On the average, increasing a BSL-2 laboratory to BSL-3 raises operating costs by about one-third; going from a BSL-3 to and BSL-4 laboratory can increase costs by a factor of three to four. Additionally, the introduction of absolute containment conditions into pharmaceutical production facilities is likely to require the development of unique equipment designs that will have a significant impact on regulatory approval processes.

conclusions:

- While there have been substantial increases in containment technology over the last years, the question still remains whether large-scale wild poliovirus production can be adequately contained when global immunity has declined.

- While the BSL-3/polio measures as currently defined provide a high degree of security under present conditions, the impact of enhancing this level of containment in a large-scale vaccine production facility on vaccine cost and capacity would be high.

WHO could undertake two additional activities to resolve this issue:

- The question of the biohazard risk level of poliovirus following the cessation of immunization should be re-examined by a group of experts specialized in the assignment of such levels. The primary question to be addressed is whether BSL-3/polio containment of wild poliovirus production at the current level of technology provides adequate safeguards against the reintroduction of poliomyelitis anywhere in the world under any state of population immunity; and

- A risk analysis of current and future wpv-IPV production and quality control facilities should be considered. This could involve a limited monitoring of operator infections through stool and/or pharyngeal secretions, and environmental sampling in the vicinity of a wpv-IPV production site.

5. Implementing adequate containment of IPV and other vaccines produced from attenuated poliovirus strains

5.1 Risks associated with attenuated (Sabin) poliovirus strains used in vaccine production and quality control

Throughout the use of oral vaccines derived from the Sabin attenuated strains it has been recognized that the level of attenuation is not absolute. Errors in genetic replication of the virus can lead to mutations with an increased neurovirulence profile, and vaccine-associated paralytic poliomyelitis (VAPP) in the vaccine recipient or a contact individual is a characteristic if very rare adverse event associated with OPV use. The global VAPP burden will amount to roughly 500 cases per year, and this would remain stable as a function of the number of OPV doses administered. The acceptability of VAPP cases is likely to decrease when the benefit of immunization against endemic poliomyelitis transmission declines following certification.

In rare cases, Sabin attenuated viruses develop both the neurovirulence and transmissibility phenotypes of wild poliovirus strains; several small outbreaks of such circulating vaccine-derived poliovirus (cVDPV) strains are now known. The analysis of these outbreaks, while preliminary and based on limited data, suggest that low-level OPV coverage combined with pockets of susceptible populations are permissive for the development of cVDPV strains. Were OPV coverage to be stopped universally, cVDPV incidence might slightly rise as susceptible populations appeared, but then would decline to zero as circulating Sabin strains were cleared. If sporadic use of OPV coverage developed or if OPV were continued in a few countries, cVDPV risks would be expected to increase. Additionally, a rare subset of persons with immune deficiency disorders have been identified that continue to excrete increasingly modified Sabin strains over months or even years, with the possibility that immunodeficiency vaccine-derived poliovirus (iVDPV) strains could become neurovirulent and transmissible. The risk of such events would depend on the level of circulation of Sabin strains in the environment. Both cVDPV and iVDPV, unlike VAPP, represent risks for the reintroduction of poliomyelitis.

Currently Sabin strains used for the production of vaccines are manufactured under BSL-1 (GMP) conditions. This is consistent with the need to protect the end-user of the vaccines and the negligible benefits that would arise from containment in vaccine production facilities when the same strains are being introduced into the environment through OPV immunization. When Sabin strains are no longer administered as live virus vaccines, however, the biohazard risk level will rise corresponding to existing or even increased risks associated with VAPP and VDPV events. In the original GAP of 1999, due to the diminished pathogenicity of the attenuated Sabin strains compared with wild poliovirus strains, BSL-2 was to be implemented one year following cessation of endemic transmission, and BSL-3 at the point when global population immunization began to decline.

The assignment of these levels was also consistent with the longer lag time needed by an AFP-dependent monitoring system to detect the endemic circulation of Sabin strains compared to wild poliovirus strains. In GAP 2003, these requirements were suspended due to the uncertainties associated with future immunization policy.

5.2 The development of new inactivated polio vaccines derived from attenuated (Sabin) poliovirus strains

Recognizing the potential of using Sabin attenuated strains rather than wild poliovirus strains as the basis for IPV, the WHO ECBS recommended that new as well as established IPV manufacturers should consider the development of Sabin-IPV (sIPV) as a replacement of wpvIPV. The virulence and transmissibility of Sabin strains is considerably less than the quickly growing wild poliovirus strains currently in use in IPV production, decreasing the biohazard risk of IPV production at the point when global immunity declines. The extensive experience with the Sabin strains as a live vaccine would also lower the regulatory expectations compared to a completely new viral strain. Under the containment requirements of the GAP 1999, even when wpvIPV was to be transferred to BSL-4, sIPV would thus be expected to remain commercially viable. For these reasons, several manufacturers are already considering the development of sIPV, with one manufacturer having applied for licensure. It is therefore timely that the biohazard risk level of Sabin attenuated strains should now be identified along with the corresponding technical guidance on the quality and containment requirements for this class of inactivated poliovirus vaccines. These guidelines will assist manufacturers in designing new production facilities and establishing product capacity and price projections, as well as their NRAs in assessing the risks and benefits involved with introducing IPV production in their countries. In most countries, the switch from wild to attenuated poliovirus strains for IPV production would define a completely new product, rather than a regulatory variation; this would equally apply to multivalent vaccines containing sIPV as an antigen. Under normal market pressures it is unlikely that such a switch would take place, and a global, coordinated approach would be needed if sIPV is to provide a sustainable alternative to maintaining wpvIPV production on a global scale.

5.3 Development of new live-virus oral polio vaccines derived from Sabin attenuated polio virus

Even if all routine polio immunization is to be stopped, an emergency response stockpile of polio vaccines to respond to unexpected outbreaks must be part of the safety precautions in place during the initial decades following certification. Currently monovalent OPV (mOPV) is the most likely vaccine candidate for the global response stockpile due to the more rapid immune response expected from the administration of a single serotype vaccine compared to the trivalent preparation, the reduction in VAPP risks by the omission of two serotypes, and the seeding of only the serotype involved in the outbreak into the environment. Sabin-based IPV (produced from mOPV bulks) may also be considered for those countries that refuse OPV vaccination or that have limited access to adequate supplies. With mOPV, sIPV, or a combination of the two, the maintenance of an emergency response stockpile of adequate size will necessitate the continued production of polio vaccines under appropriate and adequate containment conditions for many years to come. Containment of the production, testing, storage, and distribution facilities needed to maintain the stockpile must be insured even when all routine immunization has stopped. The regulatory and liability consequences of raising the biohazard risk classification of Sabin attenuated strains on their utilization as live vaccines (as mOPV) in outbreak settings also need clarification.

conclusions:

- The assignment of specific biohazard risk classifications to Sabin attenuated poliovirus strains as global immunity wanes should be conducted. This will require a detailed analysis of the risks of release of these viruses from vaccine manufacturing and quality control sites, as well as the potential public health impact of a release of an attenuated strain into an increasingly susceptible population.

- Quality guidelines for the production and quality control of Sabin-derived inactivated polio vaccine (sIPV) should be developed by WHO that incorporate specific containment guidelines for its safe production and quality control during the post-certification era for all likely scenarios of global immunization policy. The development of these guidelines include on-site assessments of current Sabin virus production sites, including developing country manufacturing sites where biosafety experience and expertise may not be as developed as in industrialized country settings.

- Harmonized requirements and approaches will be required if the large-scale wild-poliovirus production for IPV and IPV-containing vaccines is to be replaced with attenuated Sabin strain or other low biohazard starting materials.

- When vaccine-derived Sabin strains are no longer freely circulating in the environment, the production and quality control of Sabin OPV must take place within appropriate containment facilities. The biohazard risk level of OPV production would be the same as for the live-virus production areas of Sabin-IPV.

- WHO should co-ordinate the development of quality guidelines for the production and testing of monovalent OPV that incorporate containment requirements for the safe production and quality control of Sabin oral polio vaccines for the post-certification era, with primary emphasis on the construction and maintenance of global and / or national emergency response stockpiles.

- In the event that Sabin strains must be administered as a live-virus vaccine in an emergency response situation, the containment levels required for stockpile production and maintenance will no longer be considered relevant within the area affected by the outbreak, and mechanisms must be put in place to automatically reduce the biohazard risk level to that appropriate for the unrestricted use of the vaccine.

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