



# FOURTH MEETING OF THE CONTAINMENT ADVISORY GROUP



Geneva, Switzerland

<b>List of Commonly Used Abbreviations .....</b>	<b>0</b>
<b>Terms of Reference of the Containment Advisory Group .....</b>	<b>0</b>
<b>Members of the Containment Advisory Group .....</b>	<b>0</b>
<b>Session 1: Introduction .....</b>	<b>2</b>
<b>Session 2: Global update on poliomyelitis eradication and poliovirus containment ...</b>	<b>4</b>
Global update on poliomyelitis eradication .....	4
Experience and lessons learnt in facility level implementation of GAPIII .....	5
Update from the GCC-Containment Working Group.....	6
<b>Session 4: Harmonization of GAPIII requirements with other requirements, standards and guidelines .....</b>	<b>7</b>
The principles and approaches undertaken in the revision of the WHO Laboratory Manual	7
GAPIII implementation in Salk-IPV production and quality control sites (challenges in GAPIII implementation and cGMP).....	7
<b>Session 5: Supporting the implementation of ‘Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses (PIM Guidance)’ .....</b>	<b>11</b>
Issues associated with the implementation of the PIM Guidance in non-polio facilities retaining valuable clinical materials potentially infected with polioviruses .....	11
<b>Session 6: Update and follow-up issues on genetically-engineered polioviruses .....</b>	<b>13</b>
Update on past, ongoing and future plans with novel OPV2.....	13
Availability of S19 poliovirus strains and S19-Seed-lot system: Utilization in actual practice to maximize safety .....	13
<b>Session 7: Supporting the implementation of primary, secondary and tertiary safeguards as described in GAPIII.....</b>	<b>15</b>
Brief study proposal ‘Evidence-based efficacy of showering as protective measure to prevent poliovirus escape from laboratories out of the containment perimeter’ .....	15
Auxiliary exit shower for use in emergency situations preventing the otherwise use of the exit shower located at the containment perimeter.....	16
Risk-based approach to secondary and tertiary safeguards to minimize consequences of poliovirus release .....	17
<b>Additional session: Proposal for the Development of a Containment Action Plan in Support of GPEI .....</b>	<b>20</b>
<b>Session 8: Review of questions submitted to the Containment Advisory Group .....</b>	<b>21</b>
<b>Closing discussions.....</b>	<b>24</b>
Response to IFPMA and TRS 926 revisions .....	24
Future Containment Advisory Group Meetings .....	25
<b>References:.....</b>	<b>26</b>
<b>Post meeting recommendations.....</b>	<b>27</b>

## List of Commonly Used Acronyms and Abbreviations

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CAG	Containment Advisory Group
CAVA	Cold-Adapted Viral Attenuation (CAVA) - Poliovirus strains
CC	Certificate of Containment
CCS	Containment Certification Scheme (to support the WHO Global Action Plan for Poliovirus Containment, GAPIII)
CP	Certificate of participation
CWG	Containment Working Group [of the Global Commission for the Certification of the Eradication of Poliomyelitis (GCC)]
ESG	Expert Support Group [of the Containment Advisory Group (CAG)]
GAPIII	Global Action Plan for Poliovirus Containment, third edition (2015)
GCC	Global Commission for the Certification of the Eradication of Poliomyelitis
ICC	Interim certificate of containment
IPV	Inactivated poliomyelitis vaccine
NAC	National authority for containment
OPV	Oral poliomyelitis vaccine
mOPV2	Monovalent oral poliomyelitis vaccine Sabin serotype 2
nOPV2	Novel oral poliomyelitis vaccine serotype 2
OPV2	Oral poliomyelitis vaccine Sabin serotype 2
PEF	Poliovirus-essential facility
PVSRIPO	Neuro-attenuated recombinant poliovirus; live attenuated Sabin serotype 1 poliovirus with heterologous internal ribosomal entry site (IRES) of human rhinovirus type 2.
SAGE	Strategic Advisory Group of Experts on Immunization
VDPV	Vaccine-derived poliovirus (VDPV1: VDPV serotype 1, VDPV2: VDPV serotype 2 and VDPV3: VDPV serotype 3)
aVDPV	Ambiguous vaccine-derived poliovirus (aVDPV1: aVDPV serotype 1, aVDPV2: aVDPV serotype 2 and aVDPV3: aVDPV serotype 3)
cVDPV	Circulating vaccine-derived poliovirus (cVDPV1: cVDPV serotype 1, cVDPV2: cVDPV serotype 2 and cVDPV3: cVDPV serotype 3)
iVDPV	Immunodeficiency-associated vaccine-derived poliovirus (iVDPV1: iVDPV serotype 1, iVDPV2: iVDPV serotype 2 and iVDPV3: iVDPV serotype 3)
VLP	Virus-like particle
WHA	World Health Assembly
WHO	World Health Organization
WPV	Wild poliovirus (WPV1: WPV serotype 1, WPV2: WPV serotype 2 and WPV3: WPV serotype 3)



## **Terms of Reference of the Containment Advisory Group**

The Containment Advisory Group (CAG) acts as the advisory body to the Director-General of WHO and make recommendations on technical issues related to the implementation of GAPIII. The CAG is expected to provide:

1. Recommendations to WHO on technical issues arising from implementation of GAPIII;
2. Guidance on the handling of poliovirus-related materials for diagnosis, research and vaccine production (including production of VLPs, pseudoviruses, new OPV, etc.);
3. Guidance on the identification and categorization of poliovirus potentially infectious materials, their destruction, or handling and storage;
4. Guidance on the identification of acceptable alternative containment solutions in the interim period before full eradication.

## **Members of the Containment Advisory Group**

1. Professor David HEYMANN, Chair, Containment Advisory Group and Professor of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND
2. Dr Mark PALLANSCH, Director, Division of Viral Diseases, National Centre for Immunization and Respiratory Diseases, Centres for Disease Control and Prevention, Atlanta, Georgia, UNITED STATES OF AMERICA
3. Professor Shahina TABASSUM, Professor and Chairman, Department of Virology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, BANGLADESH
4. Dr Atef M ELGENDY, former [Head, Bacteriology Section and Biological Safety Coordinator, United States Naval Medical Research Unit (NAMRU-3), Cairo, EGYPT], Tampa, Florida, UNITED STATES OF AMERICA
5. Professor George E GRIFFIN, Emeritus Professor of Infectious Diseases and Medicine, St George's University of London, London, UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND
6. Dr Jagadish DESHPANDE, Scientific Consultant, Indian Council of Medical Research (ICMR) and Technical Consultant, National Task Force on Laboratory Containment of Polioviruses, Mumbai, INDIA
7. Dr Åsa Szekely BJORN DAL, Chair, NAC Sweden and Senior Expert Advisor; Biorisk management and Bio-preparedness Department of Microbiology, Public Health Agency of Sweden (PHAS), Solna, SWEDEN
8. Dr Stephen McADAM, Global Healthcare Director, DNV GL Business Assurance, Oslo, NORWAY
9. Dr Vibeke HALKJÆR-KNUDSEN, Principal Member of Technical Staff, Engineering Program/Project Lead, International Biological and Chemical Threat Reduction Program (SNL/IBCTR), Sandia National Laboratories, Albuquerque, New Mexico, UNITED STATES OF AMERICA
10. Mr Neil GODDEN, former [High Containment Specialist, Department for Environment, Food and Rural Affairs (DEFRA), Herefordshire, United Kingdom of Great Britain and Northern Ireland], UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND
11. Mr Kenneth UGWU, Senior Biocontainment Advisor, Global Affairs Canada, Ottawa, Ontario, CANADA
12. Dr Janice LO, Consultant Medical Microbiologist, Centre for Health Protection, Department of Health, HONG KONG SAR CHINA.



Monday, 15 July 2019

## Session 1: Introduction

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Michel ZAFFRAN, Director - Polio Eradication, WHO and David HEYMANN, CAG Chair

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A series of questions, submitted by the CAG, were proposed to the GPEI director, Michel Zaffran, and discussed.

1. With the continued reporting of wild polioviruses and VDPVs in samples from human and environment (so far 2019 seems not better than 2018), stringent containment requirements would seem counter-intuitive. What arguments can we deploy to advocate the need for containment?
2. The dichotomy of introducing mOPV2 for cVDPV2 outbreaks while continuing to attempt containment activities.

Discussion of (1) and (2):

- Michel Zaffran discussed that so far containment has focussed on both Sabin and wild polioviruses, and given the current epidemiology, there may be a need to separate them. For wild polioviruses, the messaging around containment is the same: there is a critical need to contain all wild poliovirus. For Sabin polioviruses, containment efforts in most regions (AMR, EUR, SEAR, WPR, EMR) can continue. However, in Africa, the programme has had no option but to place targeted holds on containment, due to the use of mOPV2 in outbreak response campaigns.
3. All along, there has been a tension on the stringency of the containment requirements. On one hand, it was considered that stringent requirements should be enforced to discourage application as PEFs. On the other, it was indicated that such requirements might appear unreasonable and not practical. Which should be the overriding principle for CAG?

Discussion (3):

- It was emphasised that there is not a clear answer to this question: we don't want countries to have too many PEFs, but it is critical to ensure a constant supply of vaccines. Michel Zaffran recommended a need to analyse whether the PEF is crucial to the programme: if deemed essential, the PEF should be encouraged, whilst still ensuring vaccine is produced in best conditions.
- A CAG member questioned whether recommendations should be made as a general scientific standard or case-by-case basis, focused on need and importance of the PEF. Michel Zaffran stated that CAG should make general advice and that the GAPIII recommendations should be applicable to all Member States, and not customised to single PEFs. However, it should be acknowledged that specific problems will arise in different countries and individual PEFs. Additionally, it is entirely feasible to state in GAPIII to outline different ways of addressing a problem.

4. Is there a need to revise the ToR for the CAG? In his report to the WHA, the DG stated that “The deliberations of the Containment Advisory Group on issues related to the implementation of GAPIII have resulted in amendments to GAPIII”. CAG is the endorsing body for documents related to GAPIII.
5. It also raises the next question that we have discussed previously but where I do not think we have received a clear answer:

What is the process for amending GAPIII? Is this purely based on the decisions made by CAG at the CAG meetings? Should there also be periodic reviews of the whole document? What are the provisions for wider consultations on any proposed amendments? Who approves the revised GAPIII?

Discussion of (4) and (5):

- The transfer of containment documents from the SAGE to the CAG was implemented as the SAGE is a programmatic advisory group and are not experts in GAPIII related matters.
  - Michel Zaffran discussed that he does not see a requirement to revise ToRs, but if the CAG members feel they are not able to deliver the ToRs, then it is possible to review them.
  - It was **confirmed that the WHO is the owner of GAPIII**. Attention has been brought to some areas of GAPIII that are not very specific, and changes/clarifications are now necessary. Therefore, the WHO expects CAG to provide guidance and advice in these areas, taken one-by-one. If the CAG recommends a change to GAPIII, the WHO will review the recommendation and if agreed, the proposed changes would be sent out for consultation and public comments. It was emphasised that this process of revision is the responsibility of the WHO.
6. Do we have working practices in the CAG that allow us to focus on the critical issues and make well informed decisions? Currently the agenda is almost entirely driven by requests from stakeholders in a rather ad hoc manner. Furthermore, decisions are often deferred by the CAG or may be made after rather limited discussions under pressure from a tight meeting agenda. CAG and WHO secretariat to discuss how this might be improved.

Post-meeting decision of (6):

- Secretariat will revise meeting approach to improve development of agenda and identify focused, critical issues for discussion.



## Session 2: Global update on poliomyelitis eradication and poliovirus containment

Global update on poliomyelitis eradication, latest GCC recommendations on containment update on the new eradications strategy 2019 – 2023.

Michel ZAFFRAN, Director – Polio Eradication, WHO

As of 15 July 2019, there have been 56 global cases of wild poliovirus in this year (compared with 33 for total year in 2018) and 83 global cases of vaccine-derived poliovirus (compared with 104 for total year in 2019).

An overview of the status of the eradication programme was provided:

### Wild Poliovirus

- WPV3 likely eradicated
- Nigeria and African Region likely wild polio free
- Pakistan/Afghanistan: continued intense transmission

### Outbreaks of Vaccine derived poliovirus

- PNG and Indonesia (type 1) likely under control
- Mozambique likely (type 2) under control
- Of concern: Horn of Africa, Nigeria and DRC cVDPV2 outbreaks (with exportations to Ethiopia, Cameroon, CAR and Angola)

The new polio-endgame strategic plan 2019-2023 was presented, with the main goals shown in Figure 1 and containment specific activities in Figure 2.

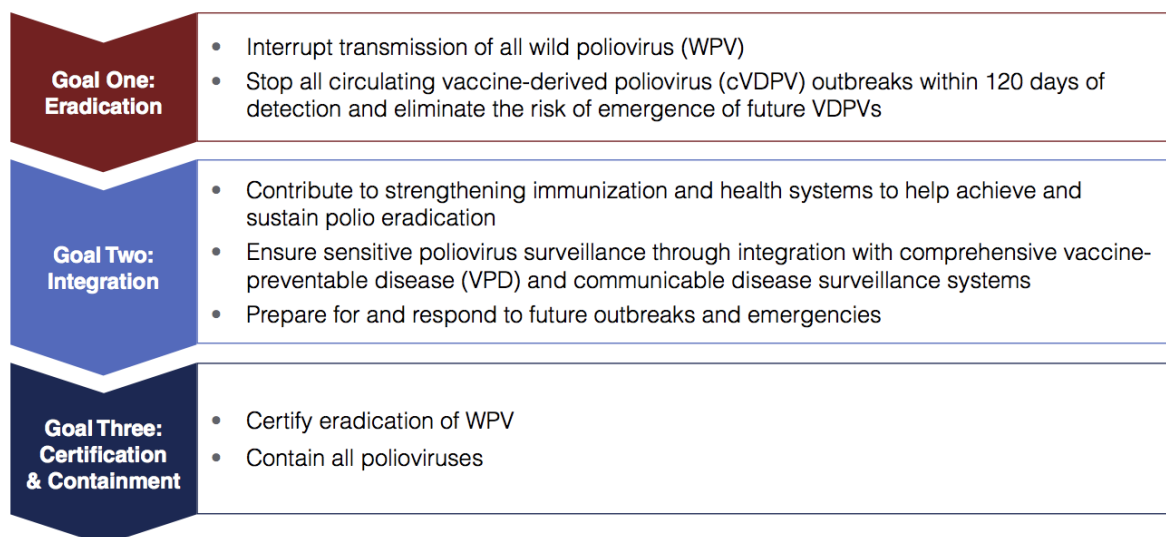


Figure 1: Goals of the Polio Endgame Strategy 2019–2023

Source: Polio Endgame Strategy 2019–2023 (Global Polio Eradication Initiative, 2019)

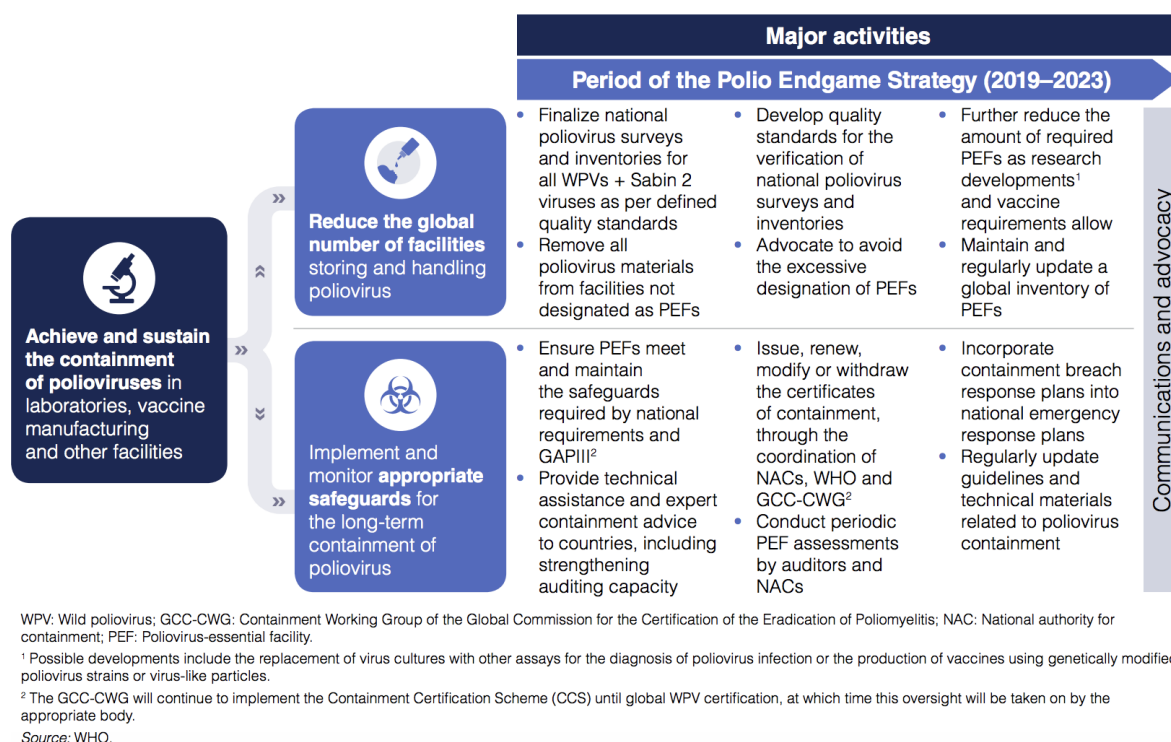


Figure 2: Containment Overview of the Polio Endgame Strategy 2019–2023

Source: Polio Endgame Strategy 2019–2023 (Global Polio Eradication Initiative, 2019)

### CAG discussion points:

- The global certification commission will first certify the eradication of wild polioviruses, then verify the absence of vaccine-derived poliovirus after complete OPV cessation.
- The post-certification strategy outlines the requirement of continued surveillance after eradication.

### Experience and lessons learnt in facility level implementation of GAPIII and its compliance verification

Åsa SZEKELY BJORNDAL, CHAIR, NAC Sweden

An overview was presented of the GAPIII-CCS training course for auditors conducted by NAC Sweden in 2018. The course took place over five days, using materials developed by WHO, comprising management system auditing training (two days) and GAPIII auditor requirements (three days). A pre-audit of the designated PEF was conducted to identify potential non-conformities to GAPIII implementation and provide a training opportunity for auditor trainees within the global network of NAC. The lessons learned included:

- The need for a plan (step-by-step scheme/process) in GAPIII-CCS.
- Auditor competencies. There is an urgent need for auditors and auditor qualifications. The suggested basic auditor qualifications were presented.
- The challenge of combining auditor training alongside PEF assessment.

- Need for a global understanding of GAPIII requirements: With regards to the more prescriptive requirements, there is a need for a common understanding of the requirement in performance-based terms. There is a risk of using the GAPIII Guidance section as prescriptive. If so, this may result in less focus on obtaining objective data on the evidence-based performance from the PEF.

## Update from the GCC - Containment Working Group

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Arlene KING, Chair, GCC- Containment Working Group

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As of July 2019, there are 77 designated PEFs within 26 PEF-hosting countries, with 25 out of 26 NACs established. The NACs have been asked to follow the schedule below when submitting applications to the GCC- Containment Working Group for Certificate of Participation (CP), Interim Certificate of Containment (ICC) and Certificate of Containment (CC) in the GAPIII Containment Certification Scheme:

- 1 December to 28 February, review by 28 March
- 1 March to 31 May, review by 28 June
- 1 June to 30 August, review by 30 September
- 1 September to 30 November, review by 17 December

To date, there have been 11 CP applications received by the GCC through established NACs, 7/11 have been endorsed and the remaining 4/11 are in the CP process. Despite an application template, there is substantial variation in the level of information that has been provided in applications. Due to the small number of applications received, there has been no requirement for rapid guidance from CAG.

### **CAG discussion points:**

- It was discussed that there is much responsibility being placed on the NACs, which will have varying levels of ability and experience.
- There is development of a cyberspace where the NACs will be able to interact with each other.

## Session 4: Harmonization of GAPIII requirements with other requirements, standards and guidelines

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The principles and approaches undertaken in the revision of the WHO Laboratory Manual

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Kazunobu KOJIMA, Scientist, Preparedness, Readiness & Core Capacity Building, WHO Health Emergencies Programme

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### Purpose of session: For information

The WHO laboratory biosafety manual (LBM) was first published in 1983 and has served the global biosafety community for more than 30 years with practical guidance on biosafety. The first edition included a classification system for biological agents (Risk groups 1-4) and laboratory classification of basic containment and maximum containment. When the first edition of the manual was published, biosafety levels had not been introduced and common diagnostic methods included virus isolation and electron microscopy. Polymerase Chain Reaction (PCR) was still in its infancy.

The current third edition was published in 2004 and incorporated biosafety levels. At the WHO extended Biosafety Advisory Group meeting in November 2014, it was deemed necessary and a priority to revise this edition. The proposed modifications to the manual were delivered to participants of the most recent extended BAG meeting in 2016 and were generally well received. The revised manual will take a risk-based approach, where risk groups and biosafety levels are replaced with a thorough risk assessment and appropriate risk mitigation control measures, based on the consequence of infection from the pathogen and the risks associated with the procedures to be carried out. This has been outlined in a position paper published in 2018 (Kojima et al., 2018). Most work will be able to be carried out using a set of four minimum core requirements: 1) codes of conduct, 2) competent and appropriately trained staff, 3) the laboratory facility/equipment and 4) good microbiological practices and procedures.

The release of the fourth edition of the WHO LBM is estimated for late 2019.

### **CAG discussion points:**

- There are several parallel manuals in development, ISO 35001, TRS 926 (subsequently named TRS 1016), LBM, where close collaboration and consistency would be beneficial. A CAG member suggested it would be useful to have a group to compare the guidance documents and determine which procedures should be followed and when in the implementation of GAPIII.

GAPIII implementation in Salk-IPV production and quality control sites (challenges in GAPIII implementation and cGMP) – 1/2

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Johan HANSELAER and Corinne BARDONE, Sanofi-Pasteur, France. Representing the International Federation of Pharmaceutical Manufacturers and Associations.

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### Purpose of session: For information

This session presented the challenges faced by Salk-IPV producers in implementation of GAPIII as well as areas requiring greater harmonization between GAPIII and cGMP.

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) members are key contributors to the Global Polio Eradication Initiative, through production, stock-piling and supply of polio vaccines. Industrial challenges consist of managing the right level of containment, minimizing the risk of polio being released into the community while maintaining supply continuity in a timely manner and rationalizing the investment and operational costs. Two specific issues were highlighted:

For quality control laboratory where multiple products (different biological agents) are tested, a product based “campaign testing” is not feasible, based on the frequency and high-volume activity within the given area. As an example, if working on three shifts, up to five hours would be used for showering out. Also, risk of potential aerosol- and mucosal transmission during showers was raised.

- Industry’s biocontainment infrastructures and stringent/documented biosafety operational practices are largely effective in minimizing poliovirus release risks. Routine showering upon exiting production/quality control does not bring any additional biosafety value; its requirement will impact industry’s ability to support GPEI.

A consultation process between IFPMA biosafety experts with WHO took place on the development of the TRS 926 guidelines. The presenter outlined that the adaptations suggested by the IFPMA biosafety experts to ensure relevance in terms of benefits/risks and feasibility by industry had been removed from the finalized TRS in three sections:

- 11.2 – QC Laboratory Requirements
- 11.5 – Sample Requirements
- 7.5 – Routine Shower Requirements

Given the current content of the TRS 926, IFPMA members have signaled that implementation of these guidelines will be difficult, to the point that this will impact their ability to meet the supply commitments made to the polio eradication program. A formal letter has been sent from the IFPMA to Emer Cooke, WHO, outlining these issues and cordially requesting the reopening of the consultation process.

### **CAG discussion points:**

- It was explained that the changes to the version of TRS 926 agreed with IFPMA were due to feedback that the text was not in alignment with GAPIII.
- The CAG stated that it takes IFPMA’s concerns seriously and will review.
- There was additional discussion over the reasons for documented accidents at Bilthoven Biologicals and GlaxoSmithKline and subsequent risk-management.

Mick BREET, Bilthoven Biologicals B.V. and Mr Dori UGIYADI, PT Bio Farma (Persero), Indonesia. Representing the Developing Countries Vaccine Manufacturers Network (DCVMN)

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Purpose of session: For information

In the first presentation by Mick Breet, Bilthoven Biologicals (Bbio), an overview was provided of Bbio and Serum Institute of India Ltd (SII). Two of the current production facilities (U4, A10 + QC lab) are not in full compliance with GAPIII physical requirements. Therefore, a new facility is being built (A7), which will be fully compliant with GAPIII, and an existing two-flow facility (A10) is being rebuilt: these two facilities have an expected output over 100M doses of IPV per year. However, current GAPIII timelines are likely to have a **serious** negative impact on IPV supply from 2021 onwards, production can only take place in the A7 facility. A concern was expressed that Bbio is not clear what is required for ICC and have a lot of questions. Additionally, the Dutch NAC is not certain on how they are going to assess Bbio. The main question Mick posed was: *“We know existing facilities will not meet physical requirements. Is it acceptable for those facilities to have an ICC certification or not?”*

Bio Farma is a PEF holding a Certificate of Participation. It is involved in the following polio activities: vaccine production, quality control testing, research and development and storage. The presentation from Bio Farma outlined the challenges in implementing GAPIII:

1. Closed sewage system (lack of)
2. Showering. There is a HEPA-filtered respirator, with showering out in the event of medium or bigger spillage and a walk-through exit shower for new facilities.
3. mOPV2 production restart. There has been a request from UNICEF for a proposal of mOPV2 restart. The facility is a GMP facility, with no walk-through exit shower, and therefore Bio Farma needs CAG advice.

**CAG discussion points:**

- What is result of NAC and WHO visits to Bio Farma? Dori Ugiyadi responded the NAC’s main comment was that Bio Farma does not have a showering system. However, there is a full HEPA-filtered respiratory system, which was accepted by the NAC.
- The role of the NAC and applications for ICC are not necessarily questions for the CAG, but the GCC-Containment Working Group.

<b>CAG recommendation:</b>
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| <ol style="list-style-type: none"><li>1. The chair concluded that it has been extremely helpful for the CAG to understand the complexity of the comments from manufacturers. He requested that Bbio and Bio</li></ol> |
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Farma provide the specific questions to the secretariat, who will deliver these to the GCC-Containment Working Group.

## Session 5: Supporting the implementation of ‘Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses (PIM Guidance)’

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Issues associated with the implementation of the PIM Guidance in non-polio facilities retaining valuable clinical materials potentially infected with polioviruses

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Miren ITURRIZA-GOMARA, Consultant Virologist for the WHO Global Rotavirus Laboratory Network (by phone)

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### Purpose of session: for decision

The Global Rotavirus Laboratory Network has developed a strategy for use among laboratories in its network to implement the PIM guidance. There are two issues identified for CAG’s guidance and recommendation:

1. Inactivation of poliovirus potentially infectious materials preserving nucleic acid integrity

It is stated in guidance documents that “*Retention of WPV/VDPV PIM is subject to the approval of responsible national authorities and requires the certified implementation of containment measures described in GAPIII. Alternatively, nucleic acids may be extracted from PV PIM or the materials may be inactivated using an appropriate method*”. However, current guidance implies formaldehyde inactivation and autoclaving as the only suitable methods. However, nucleic acid integrity is not preserved through either of these methods.

The proposal to CAG is consideration of an alternative approach to inactivate poliovirus through suspension of stool samples in chaotropic agents, which will preserve nucleic acid integrity. Specifically, the recommendation was to request to:

- Test experimentally and under controlled laboratory conditions in a PEF the ability of such lysis buffers to inactivate PV.
- Develop a method validation document that will be distributed across RV network laboratories
- Develop a simple standard operating procedure that specifies stool-lysis buffer ratio, laboratory handling and inactivated sample storage and disposal eventually.

The proposal is that any method will be co-produced by poliovirus, measles and rotavirus lab networks.

2. Excluding the presence of polioviruses from valuable rotavirus, measles and rubella virus isolates from clinical samples

Rotavirus (and other relevant ones such as non-polio enteroviruses, rubella, measles) isolates derived from clinical samples have the potential to contain WPV/VDPV. There are two proposed approaches to demonstrate that isolates are polio-free:



- Establish a repository of certified poliovirus-free viral stocks that are accessible to labs; or
- Labs could have rotavirus stocks tested and certified by the global polio network laboratories. However, this method is likely much more extensive and resource intensive.

**CAG discussion points:**

- CAG member Mark Pallansch stated that both the measles and influenza lab networks are on board with these approaches.

**CAG recommendation:**

1. The CAG recommends supporting the proposed approaches to (1) inactivation of poliovirus potentially infectious materials preserving nucleic acid integrity and (2) excluding the presence of polioviruses from valuable rotavirus, measles and rubella virus isolates from clinical samples.

## Session 6: Update and follow-up issues on genetically-engineered polioviruses

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Update on past, ongoing and future plans with novel OPV2 and other relevant research projects

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Roland SUTTER, Special Advisor to the Director of Polio Eradication, WHO

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### Purpose of session: for information

To address the goals of achieving and maintaining global eradication and minimising the risk of outbreaks of vaccine-derived polioviruses, two novel monovalent oral type-2 poliovirus (OPV2) vaccine candidates have been developed that are genetically more stable than existing OPVs, with a lower risk of reversion to neurovirulence.

The Phase 1 trial, conducted in a purpose-built containment facility at the University of Antwerp Hospital (Antwerp, Belgium), has been published (Van Damme et al., 2019). The study found that the novel OPV2 candidates were safe and immunogenic in IPV-immunised adults. Phase 2 studies - M4b Belgium (Adults) and M5 Panama (Infants) - will evaluate safety, immunogenicity, shedding and genetic stability of the two candidate vaccines. The expected date of results from one nOPV2 candidate is August 2019, and the other nOPV2 candidate in January 2020.

In December 2018, a meeting was held between the nOPV2 consortium and WHO pre-qualification team to discuss licensure, and the Emergency Use Listing (EUL) pathway, which is available whilst polio is a Public Health Emergency of International Concern (PHEIC). The best-case scenario under EUL is availability of nOPV2 in Q2 2020.

### **CAG discussion points:**

- It was discussed that if polio is removed as a PHEIC, then nOPV2 would no longer be eligible for the EUL pathway. However, Michel Zaffran confirmed that the probability of polio being removed as a PHEIC is very low.
- A CAG member asked for information on the development of polio virus-like particles (VLPs). Roland Sutter stated that work on VLPs is on-going, but there will not be a product available for use until at least 5 years. The next step is to identify manufacturers to develop large-scale commercial productions and a call for expression of interest has been sent out.

Availability of S19 poliovirus strains and S19-Seed-lot system: Utilization in actual practice to maximize safety

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Javier MARTIN, Principal Scientist, Division of Virology, National Institute for Biological Standards and Control (NIBSC), United Kingdom

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### Purpose of session: for information

An update was provided to the CAG on the availability of S19 poliovirus strains and seed-lot system. S19 strains are polioviruses that replicate in tissue culture but are unlikely to replicate at all in humans should they be exposed even to large amounts. The strains are genetically stable and include a portfolio of strains containing the capsid proteins (and thus having the antigenic properties) of the Sabin live attenuated vaccine strains or the wild strains used most commonly in the production of inactivated polio vaccine.

In December 2018, the CAG concluded that the S19 strain can be used outside of the containment requirements of GAPIII for purposes including IPV production, rat neutralization IPV potency assays, human serum neutralization test for poliovirus antibody determination and potency testing for immunoglobulin (human) lot control and release. Currently, use of S19 is for IPV production, IPV quality control, IgG quality control, serological assays and cell sensitivity.

There is a seed-lot system to produce banks of highly characterised S19 strains resembling vaccine production. NIBSC suggests that S19 strains should be tested on a seed lot basis to minimise the risks of reversion and will work with any suitable facility to help generate and validate further banks.

**CAG discussion points:**

- The CAG discussed the availability of data to assess the risk of S19 infection in humans. Mark Pallansch confirmed a) the safety data is based on animal studies and b) intended use of S19 is for IPV production, with no plan to vaccinate directly with S19. However, it was discussed that if there is an accident where the S19 strain comes out of containment, there is no data on human or environmental exposure to S19.
- S19 strains will be validated in most serologic procedures, which has already started at NIBSC and will also be done at CDC. Therefore, this will reduce number of PEFs, as many PEFs only plan to retain live poliovirus for serological assays, which will be replaced with S19 outside containment. The timeline of availability of this data was raised, as some facilities might initiate laboratory upgrades that might not be necessary. Javier Martin stated that data should be available within 6-9 months.
- It was questioned whether PEFs that only plan on conducting serology assays need to enter the CP process with NACs, if this will be able to be done outside containment. CAG advised that laboratories working with poliovirus type 2 (on serology), continue to come into the CP application process with NACs and when S19 becomes available to them, they can drop out of the process.

## Session 7: Supporting the implementation of primary, secondary and tertiary safeguards as described in GAPIII

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Brief study proposal ‘Evidence-based efficacy of showering as protective measure to prevent poliovirus escape from laboratories out of the containment perimeter’

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H.A. (Riks) MAAS and Aldo DEKKER, Department of Virology, Wageningen Bioveterinary Research, the Netherlands (by phone)

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### Purpose of session: for decision

The CAG recommendation on the showering requirement was made most recently at the CAG Teleconference on 25 January 2018, and recorded in Annex 2 and 3 of GAPIII:

*‘Controlled exit from the containment perimeter is via a walk-through exit shower. Showering out is mandatory except for facilities employing closed systems demonstrating validated primary containment. Such systems may include contained lines for use in vaccine production and/or facilities employing fully functional Class III BSCs or similar isolators. For such facilities, showering out is required as a precautionary measure, in the event of an uncontrolled breach of the primary containment equipment, during the period when further assessment of the effectiveness of showering is being undertaken.’*

The Wageningen Bioveterinary Research have submitted a project proposal which aims to provide scientific evidence on the effectiveness of showering to prevent escape of poliovirus from laboratory facilities to support WHO in deciding on biosafety protocols for laboratories working with poliovirus. The work plan has three sections:

1. Literature review:

To summarize present knowledge and gain information.

2. Risk assessment:

To evaluate the effectiveness of showering as a protective measure to prevent escape of poliovirus from laboratories.

3. Experimental studies:

The experimental studies in the project will be adapted depending on the outcome of the literature review and the risk assessment. Currently proposed experimental work is to generate quantitative data on the effect of treatment with water, soap and showering on virus infectivity and viral titres. The study proposes to use Bovine enterovirus (BEV) type 1 and foot-and-mouth disease virus (FMDV) (both picornaviruses like poliovirus) as model viruses in most of the experimental work.

### **CAG discussion points:**

- The CAG needs to decide whether they require an efficacy or effectiveness study (*effectiveness* - the way intervention is used in practice and *efficacy* - under perfect conditions) and provide Terms of Reference. The important study question to answer is whether the use of showering decreases or increases the risk of infecting the individual with poliovirus.

- The study proposal states BEV type 1 and FMDV as surrogates in experimental studies as they have biophysical similarities to poliovirus and poliovirus will be used in *some experiments*. There was concern expressed amongst CAG that the surrogate viruses were not appropriate and stated that they would require a table of the physical characteristics (e.g. stability at different humidity levels) between BEV type 1, FMDV and poliovirus from the literature, to recognise where there is a requirement for poliovirus-specific data.
- The Secretariat informed that The Polio Research Committee have funded a study proposal, titled “Use, effectiveness and risks associated with a walkthrough exit shower as a poliovirus containment barrier”, conducted by Perseus BVBA, Belgium. This design is to conduct a literature review and a survey of 10-15 high containment facilities. The results from this study will be available in October 2019.

**CAG recommendation:**

1. The CAG recommended following guidance from the existing precautionary measure recommendation, which is valid during the period that research is being undertaken. There is a research literature review and survey underway, which has been funded by Polio Research Committee and will be completed in October 2019. The CAG recommends that this research proposal is put on hold until after the results in October. If the CAG decides there is a need for more evidence, they will need to specify a research question and will approach the Wageningen Bioveterinary Research. It was also established that this research would be only the risk-analysis section of the proposal, and review would have to go through the Polio Research Committee.

[‘Auxiliary exit shower’ for use in emergency situations preventing the otherwise use of the exit shower located at the containment perimeter](#)

[Dr Stephen McAdam, CAG Member](#)

Purpose of session: for decision

Per GAPIII it is mandatory to take a shower when leaving the containment of the lab or production area. What is not described is the situation when during an emergency the normal route via the shower is not accessible and an emergency exit has to be used. Is showering out still mandatory in such an emergency? That would mean extra shower capacity in a separate fire compartment to accommodate many employees in a short period in such a way that a safe evacuation can be accomplished. The CAG was requested to provide a viewpoint on this matter.

**CAG discussion points:**

- In GAPIII, Element 10 – Emergency Response and Contingency Planning, addresses emergency planning.
- It was discussed that instead of coming directly to CAG, these issues from PEFs should first go to the NAC and through GCC containment working group.

**CAG recommendation:**

1. CAG recommended that if the PEF or NAC identify this situation as a risk, then a risk-assessment and emergency planning should be conducted. The CAG encouraged re-reading of Element 10 – Emergency Response and Contingency Planning in GAPIII.

Risk-based approach to secondary and tertiary safeguards to minimize consequences of poliovirus release

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Harpal SINGH, Technical Officer - Poliovirus Containment, WHO

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Purpose of session: for decision

This session is a follow-up on issues from the Third Meeting of the CAG, in December 2018, where issues associated with the implementation of revised secondary and tertiary safeguard requirements were raised.

Secondary safeguards – population immunity:

At the Strategic Advisory Group of Experts on immunization (SAGE) meeting in April 2018, it was recommended:

Countries with PEFs and currently using a single dose of IPV are recommended to adjust their IPV schedule, coverage targets and geographical scope as soon as possible and no later than at the time of all OPV cessation, to:

1. Implement a routine immunization schedule with a minimum of 2 IPV doses (full or fractional, standalone or in combination vaccines), with the first dose administered at 4 months and second dose at an interval of at least 4 months after the first dose.
2. Maintain high population immunity with  $\geq 90\%$  of IPV2 coverage in infants in the area surrounding the PEF defined as within a 100 km commutable distance from the PEF. Maintain the GVAP target coverage (90% national coverage and 80% in every district or equivalent administrative unit with all vaccines in national programmes, unless otherwise recommended) beyond the immediate zone of 100 km from the PEF.

Issues raised at the third meeting of the CAG are outlined as:

1. Data availability - None of the countries-hosting PEFs reported admin2 coverage data for the second dose of IPV (IPV2). IPV2 is not routinely collected.
2. Data accuracy - If proxy or closest fit indicators are reported, these are collected using the 'administrative method' which are always prone to errors
3. Age-disaggregated data
4. Cross-border collaboration when geographical extent (100 km) includes part of another country
5. Management of admin2 area (to consider part or entire admin2) when geographical extent (100 km) includes only a part of an admin2 area.

6. Interim recommendations for countries-hosting PEFs before full implementation of secondary safeguards (no later than bOPV cessation) to support the implementation of CCS.

#### Tertiary safeguards – facility and environmental controls:

Issues associated with tertiary safeguard of facility and environment controls were also presented to CAG at its third meeting: unclear definition and inconsistent approach between facilities retaining WPV/VDPV and Sabin/OPV polioviruses.

#### Proposed risk-based approach

At the third meeting CAG recommended:

*“Considering the purpose of secondary (population immunity) and tertiary safeguards (facility and environment controls) which is to minimize the consequences of a release of poliovirus, the possibility of an alternative approach i.e., the use of a risk-based approach rather than a prescriptive approach that takes into consideration the basic ( $R_0$ ) or effective ( $R$ ) reproductive rate of poliovirus in an area which depends on factors such as population density and movements, sanitation and hygiene conditions (population, environment, sewage systems and treatment), population immunity, susceptible persons, etc) should also be explored.”*

The CAG was requested to review a proposed methodology for use in a risk-based approach.

#### **CAG discussion points:**

- The CAG agreed in principle with the recommendation of SAGE on 100 km radius from the PEF vaccination coverage, but also agreed to development of a risk-based approach.
- Discussions on the various mechanisms to determine immunity levels in the area around the PEF, with suggestion of 30 cluster vaccination coverage surveys.
- The CAG agreed on pursuing a risk-based approach but did not agree to the proposed combined approach for both secondary and tertiary safeguards.
- For tertiary safeguards, the NAC will request data from government in the catchment area and conduct the risk assessment. This should include what is happening to the effluent, where is it going (closed or open system) and details of the sewage system in the community. In addition, the health and hygiene behaviours of individuals in the community should be considered.

**CAG Recommendation:**

1. The CAG agrees with the SAGE recommendation of secondary safeguards, with 90% IPV2 coverage within a 100 km radius of the PEF, as starting point.

The CAG requests the secretariat to investigate methodologies that are feasible to countries with a PEF to determine vaccination coverage in a 100 km radius of the PEF. In addition, an internal WHO assessment on what percentage of PEFs this will impact (i.e. not being able to determine vaccination coverage).

2. The CAG agrees that there needs to be a risk assessment on the tertiary safeguards in the area surrounding the PEF, which should be conducted by the NAC. This assessment should include whether the effluent system is open or closed.
3. The CAG confirmed that tertiary safeguard recommendations are specific to wild poliovirus containing PEFs and do not apply to Sabin-containing PEFs.



Tuesday, 16 July 2019

## **Additional session: Proposal for the Development of a Containment Action Plan in Support of GPEI**

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A group of CAG members met with Arlene King, Chair of the GCC-Containment Working Group to discuss proposals for the development of a Containment Action Plan in support of GPEI.

The presentation first outlined the GPEI management structure and the containment oversight and advisory bodies. There are several goals of containment (Figure 2), which are included in the various GPEI strategy plans: Endgame strategy 2013-2018, Endgame strategy 2019-2023 and Post-certification strategy. In addition, there is now sequential certification from the GCC to align with containment activities (1 - Eradication of wild polioviruses and 2 - Verification of VDPVs). It was emphasised that communication and advocacy is key. The presentation suggested that there should be a sequence of milestones for containment, which can align with the eradication sequential certification plan. This would be useful in understanding the scope/role of the CAG as time goes on.

### **CAG discussion points:**

- The definition of containment in CCS does not mention scale and could be on a macro or micro-scale. It would be useful to have a glossary on the different types of containment.
- All the confidence of assuring containment in PEFs is put on the NACs. However, there are issues related to capacity of NACs and the level of support they are getting from countries. The programme needs to be sure NACs are performing at a high standard.
- Activities of the containment working groups are fragmented (e.g. CAG, CWG, CMG). The board did not think the goals and Terms of Reference overlap across the working groups; however, alignment and awareness of the activities across the different groups is limited by capacity. There was concern expressed that the support for the activities of the GCC-CWG are under-resourced.
- Michel Zaffran confirmed that the mandate of CAG is to provide scientific evidence and advice to technical issues that arise from the implementation of GAPIII. It is not to certify containment.

## Session 8: Review of questions submitted to the Containment Advisory Group

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Inoculation step for OPV neurovirulence assay in transgenic mice critical for nOPV development and clinical assessment.

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Submission by: NIBSC, Viroclinics, PATH, Bio Farma

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The submission asks CAG to consider the proposal to carry out the intraspinal inoculation step of the TgmNVT outside a cabinet in view of an assessment of risks, the mitigating factors implemented and the potential impact of not doing so on the provision of current and new polio vaccines.

### **CAG recommendation:**

- The CAG recommends that NIBSC can continue to do this research, within the current landscape prior to CP approval. CAG recommends that the NIBSC seek an ICC for an interim period to conduct this essential research that is deemed to have a low risk.
  - Additional comments from the NAC included that the concern is the environment, and whether the room could be treated as primary containment, with a guarantee or measure to stop the virus being transported out of the room. Suggested measures included de-gowning or exit showering.

Containment requirements for the production of recombinant oncolytic poliovirus PVS-RIPO and for use in Phase II clinical trials

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Submission by: Duke University

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This is a follow up submission from Duke University, regarding production of PVS-RIPO, which is type 1 poliovirus (Sabin) vaccine carrying a heterologous internal ribosomal entry site (IRES) of human rhinovirus type 2 (HRV2). Based on available data previously submitted, CAG, at its third meeting, approved PVS-RIPO for use in phase II cancer immunotherapy clinical trials outside of the containment requirements of GAPIII. However, CAG requested the submission of additional data by applying the ‘Criteria for the evaluation of improved ‘safety’ of novel PV strains to determine the containment needs for their storage and handling’, particularly as it relates to shedding studies on treated patients. Of concern to CAG was the production phase of PVS-RIPO as information was limited, and additional information was requested.

### **CAG discussion points:**

- The CAG was satisfied with the additional information that was provided, which addressed the questions the CAG requested.
- The CAG additionally felt that this was a very promising oncolytic treatment which would have significant public health importance if effective.

<b>CAG recommendation:</b>
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1. CAG recommended that production of PVS-RIPO can continue outside containment.

## Biocides

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### Submission by: Dutch National Authority on Containment

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The submission by the Dutch NAC requested the CAG to provide a list of validated disinfectants that can be used in laboratory settings and are effective against poliovirus.

#### **CAG recommendation:**

1. The Global Polio Laboratory Network (GPLN) small working group has created a guidance document on poliovirus inactivation, which should be available shortly and will be on the WHO website. The CAG refers to the GPLN guidance document as a reference.

### Storage outside containment – permitted with CP, ICC and CC (i.e. phase II and III).

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The question submitted to the CAG: what are the requirements in GAPIII that are applicable to storage-only facilities?

#### **CAG recommendation:**

1. Storage-only facilities should be compliant to all requirements from GAPIII. Any exceptions the facility needs should be outlined to the NAC with a risk assessment.

## Poliovirus-dedicated facilities

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### Submission by: Canadian National Authority on Containment

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GAPIII requires that poliovirus materials be handled in a poliovirus-dedicated facility but makes no distinction between facilities handling high titre or volumes (e.g. vaccine production facilities) and those handling low titre or volumes (e.g. diagnostic, research and QA/QC laboratories). In December 2018, a request was received that the requirement be dependent on the scale and use of poliovirus materials and to recognize the distinction between laboratory scale (diagnostic, QC/QA) work and production scale risk mitigation i.e., at laboratory scale, where all materials, equipment and waste are treated as though they contain poliovirus and are all subject to GAPIII requirements, a dedicated facility may not be required.

At its third meeting, CAG recommended:

*CAG's previous recommendation on the issue of non-dedicated poliovirus facilities is not changed. However, CAG urges the secretariat to reach out to the submitting NAC to gather additional information on this request in time for the next CAG meeting*

The Canadian NAC responded with additional information on this request.

*“We recognize that the GAPIII allows for facilities to be used on a “campaign basis” with effective decontamination in between. However, we are proposing that the laboratory-scale poliovirus facilities, provided all decontamination methods and procedures as per GAPIII are implemented, may also conduct on-going work with pathogens other than poliovirus in a “multi-purpose laboratory suite”. As such, laboratory-scale activities should not require the facility to be dedicated or only used on a campaign basis, but to conduct poliovirus work, along-side other pathogens, provided all GAPIII procedures are fully implemented for all areas of the multi-purpose laboratory suite, regardless of the organism in use, during all phases of GAPIII. We are not proposing that the same flexibility be provided to large scale vaccine production as we recognize the unique risks associated with large volumes and scale.”*

**CAG discussion points:**

- There is an agreement by bio risk experts that operating single-agent facilities significantly reduces risk. The biggest concern is multi-agent research facilities rather than GMP controlled vaccine production facilities.
- The CAG agreed that there must be a risk-assessment conducted by the NAC.
- The CAG highlighted that this is one of the three issues raised by the IFPMA, and that it (CAG) needs to deliberate this seriously and respond.
- See end of report for post-meeting recommendations.

## Closing discussions

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### Response to IFPMA and TRS 926 revisions

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The WHO secretariat will draft a reply to IFPMA, addressing each of its three issues, with the suggested amendments based on CAG discussions. This will be circulated amongst CAG members for approval. The response letter will then be sent from Michel Zaffran to Ms Emer Cooke, Regulation of Medicines and other Health Technologies, WHO. [The recommendations are in the post meeting section of this report].

Specific discussion points are outlined below:

#### 11.2 – QC Laboratory Requirements [see post meeting recommendation]

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##### **WHO/BS/2018.2350** (last TRS draft of May 2018 with WG proposal)

- **11.2** The use of non-dedicated quality control laboratories may be permissible under the following conditions:
  - The non-dedicated quality control laboratories are located within the containment facility.
  - All non-poliovirus-related activities performed within the containment laboratories and all personnel admitted into the containment laboratories adhere to all applicable containment procedures.

##### **Post-ECBS 9 Nov 2018** (finalized version issued in November 2018)

- **11.2** The quality control laboratories operating under containment conditions should be either poliovirus dedicated or used on a campaign basis using validated decontamination procedures per CAG recommendation (29).

##### **CAG discussion points:**

- The CAG delegated CAG member Stephen McAdam to work with the secretariat on the wording of 11.2 and after agreement, the CAG will recommend this change to GAPIII.
- Specific comments were modifications to **WHO/BS/2018.2350** a) changing *adhere to all applicable containment* to *compliant with GAPIII* and b) add a bullet point about risk mitigation.

#### 11.5 – Sample Requirements [see post meeting recommendation]

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##### **WHO/BS/2018.2350** (last TRS draft of May 2018 with WG proposal)

- 11.5 Samples received from the containment areas should be handled using established procedures to prevent the release of live poliovirus.
- Procedures used to decontaminate sample containers or packaging materials should be validated and shown to have no impact on sample integrity. The packaging materials should be decontaminated prior to disposal.

- All samples received from the containment production facilities, with the exception described below in section 11.5.1, should be tested in containment laboratories.
- All test procedures using reagents containing live poliovirus should also be performed within the containment laboratories.
  - 11.5.1 Certain samples (such as those for water and environment monitoring) taken from the containment areas may be tested outside the containment laboratories if a risk assessment concludes that they are unlikely to contain live poliovirus, based on facility design, equipment used (especially closed system) and sampling locations. However, necessary precautions covering sample handling, transportation and disposal may be recommended based on the risk assessment.

**Post-ECBS 9 Nov 2018:** 11.5.1 removed

**CAG discussion points:**

- The CAG agrees with the concept of 11.5.1 in **WHO/BS/2018.2350** and request the secretariat to work out what changes need to be in GAPIII.
- CAG suggested the wording: *“Certain samples can be taken from the GAPIII polio containment areas and may be tested outside the polio containment labs if a risk assessment concludes they are unlikely to contain poliovirus, based on factors such as facility design, equipment used (especially closed system) and sampling locations.”*

[7.5 – Routine Shower Requirements \[see post meeting recommendation\]](#)

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**WHO/BS/2018.2350** (last TRS draft of May 2018 with WG proposal)

**7.5.6** A full-body shower should be available within the personnel exit airlock from the containment area. The use of a shower upon exit should follow an established procedure supported by the risk assessment and consistent with policies established by GAPIII and CAG recommendations.

**Post-ECBS 9 Nov 2018** (finalized version issued in November 2018)

**7.5.6** A full-body shower should be available within the personnel exit airlock from the containment facility. The use of a shower upon exit should follow the policies established by GAPIII and CAG recommendations.

**CAG discussion points:**

- The CAG suggested modification to the wording of 7.5.6 in **WHO/BS/2018.2350**: *‘...supported by the risk assessment in accordance with element 2 ..., as a temporary measure and until such time that the evidence is completed on the risks and benefit of showers.’*
- CAG member Neil Godden will provide a written draft to the secretariat to circulate.

[Future Containment Advisory Group Meetings](#)

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**CAG recommendations:**

1. CAG recommends that the secretariat will decide whether questions come directly to the CAG or go through NACs and GCC-Containment Working Group. At the minimum, the NAC needs to be copied in on correspondence coming from PEFs.

Additionally, future requests to CAG should be compiled and analysed before bringing to the CAG meeting.

**Fourth Containment Advisory Group Meeting**

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A teleconference for the next Containment Advisory Group Meeting was suggested.

Agenda items include:

1. Mark Pallansch to present views on guidance of potentially infectious materials (PIM)
2. Neil Godden to present on dedicated air handling systems
3. Mr Kenneth Ugwu to work with secretariat and present on effluent systems

**References:**

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- WHO EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION: SIXTY-NINTH REPORT. Geneva: World Health Organization; 2018 (WHO Technical Report Series, No. 1016).

## Post Meeting Recommendations

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With regard to the concerns raised by IFPMA and the revisions to TRS 1016 (previously TRS 926), the following recommendations are made to address the routine shower requirements, dedicated versus non-dedicated QC laboratory issue, and the sample requirements for testing outside containment:

*A full-body shower should be available within the personnel exit airlock from the containment area. The requirement for personnel to take a shower during the exit process from the polio containment facility until eradication is declared shall be according to the relevant specific risk assessment undertaken by the facility and agreed to and accepted by the National Authorities for Containment (NACs). This risk assessment shall be undertaken in accordance with GAP III, especially Element 2 - risk assessment. The risk assessment shall address foreseeable and credible scenarios as required by GAP III - Element 10. Thus, the interpretation of the implementation of routine showering-out is left to the discretion of the NAC. This follows the submission of a documented and detailed risk assessment for the NAC to consider. Changes in any associated circumstances must be reported to the NAC and where needed the submission of a new risk assessment. [Given that there is no PV specific evidence to support or refute the shower issue, language has been developed which places the onus on the PEF. Showering out is optional but subject to stringent facility-led risk assessment. The PEFs are solely responsible for any potential mishaps – any breaches from perimeter without use of a shower are due to poor risk assessment in the PEF]*

*On the issue of dedicated versus non-dedicated quality control laboratory, non-dedicated (multi-pathogen) quality control laboratories may be permitted if they are located within the containment facility and non-PV related activities performed within the containment laboratories and all personnel entering those labs comply with GAP III recommendations.*

*On the issue of handling samples outside the containment facility-- certain samples (i.e. those for water or environment monitoring) taken from within the containment perimeter may be tested outside the containment labs if a risk assessment concludes that they are unlikely to contain live poliovirus, based on facility design, equipment used (especially closed systems) and sampling locations provided all sample handling, transportation, and disposal processes adhere to GAP III.*