

## CAG Teleconference

20 March 2020

Attendees: Chair David Heymann, Mark Pallansch, Stephen McAdam, Vibeke Halkjaer-Knudsen, Neil Godden, Ken Ugwu, Atef El-Gendy, Shahina Tabassum

Excused: George Griffin, Asa Szekely Björndal, Jagadish Deshpande, Janice Lo

WHO: Secretariat Daphne Moffett; Nicoletta Previsani

External participants for presentation of issues: John Konz, PATH; Andrew Macadam, NIBSC; Jennifer Anstadt, US CDC.

### Issue/Question/Proposal to the CAG:

1. Does CAG agree that chimeric novel OPV viruses, which employ a type 1 or type 3 capsid and modified type 2 non-structural region, should be considered as type 1 or 3 viruses for the purpose of containment regulations?
2. Does CAG agree that, as was decided for the nOPV2 strains, the four type 1 and 3 novel OPV viruses described herein are suitable for handling outside the GAPIII containment requirements for the purposes of production (of specified strain), quality control testing, and clinical trials?

Four novel OPV strains against types 1 and 3 poliomyelitis are currently being manufactured for clinical development, with similar aims as the nOPV2 project. Questions have arisen associated with the regulation and control of these viruses for the purposes of manufacturing and clinical development. CAG's concurrence on two topics was sought, with the proposed positions stated below.

### **Topic 1. For the purposes of containment, novel OPV strains should be defined by their capsid regions**

Background for question: The Dutch bureau on GMOs has asked for a formal position whether the presence of type 2 non-structural regions in a modified, attenuated poliovirus with a type 1 or 3 capsid should require containment as a type 2 virus for GAPIII purposes.

Position:

In order to leverage the non-clinical and clinical experience developed from the nOPV2 project, the nOPV1 and nOPV3 candidates were developed utilizing the nOPV2 candidate 1 non-structural regions, or slightly modified versions thereof, and replacement of the capsid (P1) region of the virus with the relevant Sabin-1 or Sabin-3 region.

By definition, we understand poliovirus type to be identified by its capsid. Therefore, we submit that chimeric viruses which employ non-structural regions from Sabin-2 or nOPV2 but a type 1 or 3 capsid should be defined as type 1 or 3 for containment purposes. The definitions in GAPIII support this position under Poliovirus, OPV-like where it identifies “included materials” as follows:

- derivatives produced in the laboratory that have capsid sequences from OPV/Sabin strains;
- full-length RNA or cDNA that includes capsid sequences derived from OPV/Sabin strains;
- cells persistently infected with poliovirus strains whose capsid sequences are derived from OPV/Sabin strains.

Omitted under this list, the similar list under WPV, and other discussion in GAPIII is any indication that the non-structural regions are to be used to identify a derivative as a particular poliovirus type for the purposes of containment. It is inferred from this omission that inclusion of type 2 non-capsid poliovirus regions into a derivative should not be grounds for consideration of the derivative as requiring type 2-specific containment procedures. The same reasoning explains why cVDPV2 strains are not identified as non-polio enteroviruses, despite often containing non-polio enterovirus non-structural regions acquired through recombination. CAG’s confirmation of this position is sought, either generally or specifically for the four viruses we describe in Topic 2 and Annex 1.

## **Topic 2. Consideration for exclusion of development and production activities for nOPV1 and nOPV3 strains from GAPIII**

The four nOPV1 and nOPV3 candidates which are currently undergoing manufacturing and quality control activities with the intent to study clinically are summarized in annex, including data on attributes that the CAG has stated are relevant for the consideration of novel, genetically-stabilized strains. GAPIII is clear that both WPV and OPV/Sabin viruses are not anticipated to be handled under strict GAPIII containment until wild polioviruses (WPV) are declared eradicated (Figure 1, p. 9 of GAPIII). The recent position statement issued by GPEI states that with certification of WPV3 eradication WPV3 and VDPV3 (but not Sabin OPV3) should now be included in containment provisions. Outside the introduction, GAPIII does not address novel, genetically stabilized strains; however, the definition of wild-type strains (definition of “Poliovirus, wild” on p. 24 includes strains not licensed for use as live vaccines) could be considered, perhaps resulting in nOPV3 strains being considered as wild-type by some regulators in absence of CAG guidance.

With these considerations in mind, CAG’s input is sought on the position that the data from these four strains, along with the clinical data for the nOPV2 candidate 1 strain on which they are

based, is sufficient for exclusion from GAPIII. In the event that the data are not considered sufficient, advice is sought as to appropriate handling conditions, considering that some national authorities may default to expectations for wild-type virus in this case, which will likely delay and perhaps prohibit advancement of the candidates into clinical testing.

#### Risks:

There is no evidence of unique risks associated with the manufacturing or clinical use of the novel strains described. The information in Annex 1 suggests that the risks of exposure are likely to be reduced as compared to the Sabin strains.

For manufacturing activities, risks will be mitigated as for current Sabin-1 and -3 strains, generally through handling at Biosafety Level 2. For clinical studies, the Phase 1 study is planned for a location with high polio vaccination coverage and good sanitation and hygiene. Inclusion/exclusion criteria will be in place to ensure protective polio titers for recipients in the Phase 1 study, exclude individuals with immunodeficiency, and exclude individuals who may routinely come in contact with immunodeficient or unvaccinated individuals. A draft synopsis for the Phase 1 trial can be made available on request.

#### **CAG Recommends the following:**

Issue 1: The capsid does define the poliovirus type. Chimeric viruses which employ non-structural regions from Sabin-2 or nOPV2 but a type 1 or 3 capsid should be defined as type 1 or 3 for containment purposes. There has been high consistency on defining types based upon the capsid sequence with precedence of more than 30 years. CAG agrees with the proposal to consider types 1 and 3 only on the basis of the capsid sequence and not subject to type 2 containment. Note: this is a transitional recommendation as its impact on containment. These viruses are not subject to type 2 containment even though they contain sequences in the non-capsid region that are derived from Sabin 2 since that has no effect on the type of poliovirus. Sabin 1 and 3 are still used in routine immunization. However, once type 1 and 3 containment guidelines are issued, the expectation is that GAPIII guidance for Sabin viruses would apply.

Issue 2: There is complete analogy with previous nOPV2 construct discussions. Primary difference being insertion of capsid sequences from type 1 and type 3. Data were analogous to that presented for nOPV2 and show same *in vitro* properties that are consistent with what was discussed with type 2. Containment of type 3, or both type 1 and 3, will be implemented at some point in the future after OPV cessation. At this time, this recommendation represents a preemptive step to address concerns raised by regulators. Consistent with previous deliberations, CAG agrees with handling these 4 new candidate strains (1 and 2) for types 1 and 3 outside of GAPIII containment for purposes of production, quality control testing and

clinical trials as indicated. Handling of infectious materials within facilities within countries is subject to oversight of national and international regulations and those country-specific regulations maintain primacy.