CAG TC2 on Novel Poliovirus Strains
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Report

Participants:

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Issue 2: Novel poliovirus strains

Relevant GAPIII Section

Introduction (last sentence, last paragraph):
Although Annexes 2 and 3 are written specifically for wild polioviruses and OPV/Sabin strains, respectively, as they exist at the present time, should novel strains emerge that are considered to be more attenuated, less pathogenic and safer than OPV/Sabin strains, the evidence will be reviewed by a panel of scientific experts convened by WHO to consider the controls applicable to their containment and safe handling.

History

Summary of requests to CAG1

Encourage newer safer technologies or newer strains for the production of polio vaccines and diagnostic reagents, and determine appropriate containment requirements for the handling of specific strains (e.g. S-19 Sabin2 containing Sabin2 capsid sequence; nOPV strains).

CAG1 recommendation

Create a CAG Expert Support Group (CAG-ESG) to consider containment requirements for the new strains and propose potential solutions to the CAG and other groups if necessary, for review and approval.

CAG2 recommendation:

In order for CAG to determine the containment requirements for novel Sabin strains, the CAG-ESG needs to look at available data on genetic stability, reversion, behaviour in the environment and in-vivo human studies, and determine what additional data are required. Based on these, the CAG will make a position statement.

CP applications should address work with novel strains. NACs and the GCC-CWG may ask CAG for guidance before issuing certificates.

CAG TC2 on novel poliovirus strains addressed the following 3 agenda items:

a. Criteria for evaluating improved 'safety' of new poliovirus strains
b. CAG-ESG assessment and conclusions on containment requirements for the S19 strains
c. CAG-ESG assessment and conclusions on containment requirements for nOPV2 strains for vaccine production

a. Criteria for evaluating improved 'safety' of new poliovirus strains

Background

In advance of the TC, CAG-ESG were requested to begin the development of draft criteria necessary for the evaluation of every novel poliovirus strain with regard to safety and to determine appropriate containment requirements for storage and handling.

Proposed criteria

CAG-ESG proposed information be provided on 3 essential criteria for evaluation of novel poliovirus strains:

1. Neurovirulence
2. Genetic stability to loss of attenuation
3. Replicative fitness

For each of the criteria, appropriate lines of evidence required to demonstrate the criteria had been met were outlined and discussed.

Summary of CAG TC2 discussions and conclusions:

a. The proposed criteria and their component lines of evidence required were discussed by CAG, resulting in agreement that the criteria were appropriate.
b. Lines of evidence required to demonstrate a novel virus meets the criteria are almost exclusively available through data obtained from *in vitro* and animal studies. Concerns were expressed that for some proposed novel strains animal data is not yet available. Detailed SOPs for obtaining this data are available.
c. Concerns were raised that any risk assessment of a novel poliovirus strain should not be restricted to characteristics of the virus itself but expanded to include assessment of the uses intended for the virus, since overall risk is dependent on use. Some intended uses (as an oral polio vaccine, for example) may fall outside of the mandate of CAG and recommendations from the CAG should focus primarily on containment requirements within polio facilities.
d. The application of risk assessment based on the proposed criteria permit novel poliovirus strains to be excluded from GAPIII Annex 3 containment requirements if agreement from the NAC is obtained. However, concerns were raised over the apparent absence of a mechanism to reestablish the necessity for a strain to meet Annex 3 requirements should events transpire, usage change or the original risk assessment be deemed inadequate. Concerns were also raised on current surveillance capacities to detect these new strains.

In conclusion, CAG agreed with the proposed criteria and lines of evidence required but noted that any risk assessment of a novel strain should include an assessment of risk associated with intended use of the virus. In addition to the criteria, guidance to national authorities, vaccine manufacturers and laboratories on the expected scope of any risk assessment and how to use the criteria for the assessment of novel strains would also be required.

Recommendations:

1. Criteria for risk assessment of novel poliovirus strains should continue to be developed together with guidance for use. Formal mechanisms for CAG to evaluate and comment on risk assessments based upon these criteria should also be developed.
2. WHO/CAG should develop a brief white paper on what is expected from countries in terms of risk assessments, with reference to the proposed criteria, for distribution to all NACs.

b. CAG-ESG assessment and conclusions on containment requirements for the S19 strains

Background

Submission has been made for CAG to approve the use of S19-Sabin2 (containing Sabin 2 capsid sequence) at a lower level of containment than that recommended for type 2 poliovirus under GAPIII. At its second meeting CAG recommended the CAG-ESG should evaluate available data on attenuation, genetic stability and behavior in the environment and *in vivo* studies, in order for CAG to determine if sufficient evidence was available, or additional data required, for CAG to conclude on the containment requirements for the S19 strains.

Summary of CAG TC2 discussions and conclusions:

a. Evidence has been provided for the mechanism and extent of attenuation and genetic stability of the two, very similar, S19 strains that are being proposed. Extensive data on infectivity and stability at physiological temperatures *in vitro* and in the mouse model are also available.

b. There is a theoretical low risk that attenuation could be lost through recombination with other polioviruses or non-polio enteroviruses should co-infection in humans occur. Infectivity for humans is claimed to be very low, but *in vivo* evidence is lacking. There is data on infectivity following oral administration to non-human primates, demonstrating a very limited period of virus shedding in stools.
c. The S19 strains are now being used in two countries, with application in process in a third, including for production of IPV without adherence to Annex 3 requirements. Use of the strains has been licenced for vaccine production under national regulations, although details of the risk assessment process have not been made available to CAG. It remains unclear to what extent the National Authority for Containment (NAC) has been involved in assessing the containment requirements.

In conclusion, although a considerable amount of technical information on the S19 strains has been made available, more details are required on the process, extent and results of the risk assessments that have been conducted before CAG can come to any decision on the level of containment recommended for vaccine production compliant with GAPIII. All relevant authorities should be made aware that CAG will require risk assessments not only of the novel strains proposed, but also of the intended uses to which they will be put.

Recommendation:

1. WHO secretariat to contact the relevant national authorities with a request to provide:
   - details, including the scope, process used and results obtained, of the risk assessments conducted for containment requirements of S19 strains for IPV production and how the risk assessments conducted relate to the assessment criteria proposed by CAG-ESG;
   - current containment conditions used to produce, handle and store the S19 strains prior to inactivation.

   The request should specify the timeframe in which a response is expected.

c. CAG-ESG assessment and conclusions on containment requirements for nOPV2 strains for vaccine production

Background

Two nOPV2 strains have been developed as candidate vaccines, and some attenuation and genetic stability data has been published on both. Unlike the S19 strains, these strains have been developed for use as live oral vaccines. The attenuation strategies have been demonstrated to be highly effective and stable *in vitro*, and a phase I human clinical trial has provided *in vivo* data demonstrating infectivity. Some of the genetic stability data from the phase I trial is, as yet, incomplete.

Summary of CAG TC2 discussions and conclusions:

a. Technically, at present, these viruses should be contained under GAPIII Annex 3 requirements, but they have been used as live oral vaccines given to humans in a phase I trial in enclosed facilities under 'contained' conditions. Additional data on the phase I trial is expected in April. There is intention to conduct the next phase of the study in two countries under non-enclosed conditions, which, technically, would be in breach of GAPIII Annex 3 requirements.
b. Decisions to conduct the next phase of study of these strains in vaccine trials have been made at country level. Requests have been made to WHO for recommendations on containment requirements for future trials. Following receipt of the additional information from the completed phase I trial in April, or later if delayed, the CAG will be requested to consider recommendations for containment requirements for future trials of these strains as oral vaccines.

In conclusion, it is beyond the mandate of CAG to make recommendations on containment requirements for virus strains that are being utilized as live oral vaccines. It is the responsibility of national authorities to conduct the risk assessments and decide on use of a particular vaccine strain, but it is in the interests

of CAG to establish logical consistency with the containment requirements for production of these strains. Further data on the phase I trial will be available in April and CAG will be asked to consider the containment status of nOPV2 strains following receipt of that information.