The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POSITION PAPER ON VIRAL SAFETY OF ORAL POLIOVIRUS VACCINE (OPV)

1. Viral risk from OPV grown on primary monkey kidney cell substrates when alternative cell line substrates are available

OPV grown on primary monkey kidney cell substrates is widely used in Member states and elsewhere in the world. OPV grown on well characterised human diploid cell or Vero cell lines is also licensed, available and used in several EU member states.

The potential risk of adventitious viruses entering the manufacturing process is different for each cell substrate. Requirements (1,2) have been in place for many years and have been regularly updated and are designed to eliminate known risks whatever cells are used. In particular for primary monkey kidney cells each individual animal is pre-screened for seronegativity to SV40 and SIV and each donor animal must remain healthy throughout a quarantine period. The cells from each donor animal are also tested for a broad spectrum of adventitious agents.

Rigorous adherence to these requirements by OPV manufacturers, plus the use of animals from closed or intensively monitored colonies, results in harvests from primary monkey kidney cells that nowadays very rarely fail adventitious agents tests.

Poliovirus vaccines are subject to independent assessment in the EU batch release procedure. Batch protocols are reviewed by OMCL experts before official release of each batch of monovalent polio bulk. This includes critical review of the pre-screening and adventitious agents test results.

Taken together these procedures give an assurance that batches of OPV derived from primary monkey kidney cells released for use by OMCLs are safe from viral risk.

2. The safety record of OPV

OPV manufactured in primary monkey kidney cells has been the major source of vaccine in the majority of European countries for about 35 years. Vaccine associated poliomyelitis is a recognised but very rare adverse event due to reversion of the vaccine virus. Otherwise OPV has an exemplary safety record.

It is well known that very early batches of inactivated poliovirus vaccine (IPV) grown in primary monkey cells were contaminated with SV40. However, OPV was not introduced until after this discovery. Effective measures were rapidly put into place to exclude live SV40 from the very beginning of OPV usage. Currently used IPV is not contaminated with SV40 and a recently published definitive epidemiological study (3) shows that after more than 30 years of follow-up SV40 contaminated IPV is not associated with an excess of cancer in humans.

3. The possibility of introducing PCR testing of OPV for SV40 and/or SIV

SV40 sequences of unknown origin have recently been detected in several rare human tumours. In the light of these findings, NIBSC considered it would be prudent to confirm that the precautions in place to exclude live SV40 from OPV are effective when tested by a sensitive and specific PCR test for SV40. A suitable test was developed and used to screen all available monovalent bulks in the NIBSC archive. This represented all monovalent bulks used in one member state since 1980 and many from the period 1966-1979.

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The results were given to the February 1998 Biotechnology Working Party (BWP) meeting (4) and have been submitted for publication and are summarised again here.

None of 133 bulks repeatedly and exhaustively tested had detectable SV40 sequences and it was concluded that the steps taken to ensure that OPV is free of live SV40 are satisfactory. This and other data were presented at a WHO Informal consultation on SV40 and poliovirus vaccines in September 1997 and at the WHO Expert Committee on Biological Standardisation (ECBS) in October 1997. Both meetings agreed with the conclusion that live SV40 had been effectively excluded from OPV. Reports of the WHO meetings were presented to the BWP (5,6).

One OPV seed virus from 1962 was found to contain SV40 sequences by PCR. In 1962 the manufacturer had found live SV40 in this material by tests in cell culture and had treated the seed to specifically inactivate DNA viruses. Studies at NIBSC on this seed material showed that infectious SV40 could not be demonstrated and there was no detectable risk of virus transmission. The PCR test for SV40 therefore confirmed what was already known from cell culture tests.

If introduced, PCR for SV40 would have to be used as an additional test on monovalent polio bulks since the cell culture tests currently in place are sensitive to a much wider spectrum of potential viral contaminants. The broadly reactive cell culture tests could not be replaced by highly specific PCR. Recent data from NIBSC also suggests that PCR is no more sensitive for SV40 than cell culture assays. Furthermore to facilitate between laboratory comparisons of PCR tests suitable working reagents (e.g. run controls) would be required and would need development work.

Taken together, these results and considerations show that routine testing of monovalent polio bulks by PCR for SV40 is achievable, but it is not more sensitive than current procedures for detection of live SV40 in OPV. Therefore the BWP does not recommend the introduction of routine PCR for SV40 and also suggest that current procedures are satisfactory and should continue to be used.

NIBSC and others have also examined monovalent polio bulks for SIV sequences (7,8). These studies found no evidence of SIv sequences in archived monovalent bulks manufactured in primary monkey kidney cells before the discovery of SIV and the introduction of screening procedures. Furthermore it was shown that SIV was unlikely to survive the procedures involved in the production of monolayer substrates or to replicate under the conditions required for the growth of poliovirus.

These results show that routine testing of monovalent polio bulks by PCR for SIV is also achievable but that tests of monovalent bulks are not indicated. However, manufacturers may wish to investigate the use of PCR to screen individual animals or colonies to complement the biological tests already in place.

4. Are Ph. Eur and/or WHO Requirements adequate

The requirements are adequate but consideration should be given to use only animals from closed or intensively monitored colonies to derive primary monkey kidney cells for OPV production. Consideration should also be given to exclude, in addition to live SV40, inactivated SV40 sequences from OPV and IPV virus seeds. The WHO Expert Committee on Biological Standardisation agreed to consider the latter proposal in 1998. The Ph.Eur Group 15 meeting discussed exclusion of SV40 sequences from OPV and IPV seeds on 31 March 1998 and also agreed to consider this proposal further.

5. Conclusions

a) The BWP agreed that primary monkey kidney cells remain an acceptable and widely used cell substrate for production of oral poliovirus vaccines provided that current requirements to exclude viral contaminants are fully implemented.

b) There is no evidence for transmission of either SV40 or SIV from oral poliovirus vaccines that meet current WHO and Ph Eur Requirements and are manufactured to relevant GMP principles.

c) An intensive survey of 133 poliovirus bulks from 5 manufacturers dating back to 1966 by a sensitive and validated PCR in one Member State showed that no SV40 sequences were detected. More limited studies on SIV also reached the same conclusion.

d) The WHO and Ph Eur should consider a requirement to use only animals from closed or intensively monitored colonies to derive primary monkey kidney cells for OPV production. Also a requirement to exclude, in addition to live SV40, inactivated SV40 sequence from OPV (and IPV) virus seeds should be considered.

6. References

1) WHO Requirements on use of animal cells as in vitro substances for Biologicals production.

2) Cell substrates for the production of vaccines for human use. Ph Eur.

3) Strickler H.D; Rosenberg P.S; Devesa S.S et al. Contamination of poliovirus vaccines with Simian Virus 40 (SV40) (1955-1963) and subsequent cancer rates. J. Amer, med. Assocn (1998), 179, 292-295.

4) Position paper to February 1998 BWP meeting: oral poliovirus vaccines and SV40 sequences. EMEA.

5) Report of a WHO Informal Consultation on SV40 and Poliovaccines, WHO, Geneva. 18 September 1997.

6) Draft report of 1997 WHO Expert Committee on Biological Standardisation.

7) Garrett A.J; Dunham A and Wood D.J. Retroviruses and poliovirus. Lancet (1993), 342, 932-3

8) Khan A.S; Shahabuddin M; Bryan T et al. Analysis of live, oral poliovirus vaccine monopools for human immunodeficiency virus type 1 and simian immunodeficiency virus. J. Inf. Dis (196) 174, 1185-90