WORLD HEALTH ORGANIZATION
ORGANISATION MONDIALE DE LA SANTE

REQUIREMENTS FOR THE USE OF ANIMAL CELLS AS *IN VITRO* SUBSTRATES FOR THE PRODUCTION OF BIOLOGICALS

(Addendum 2003)

Introduction

WHO Requirements for the use of animal cells as *in vitro* substrates for the production of biologicals (1) provide information on a WHO cell bank of Vero cells. These cells were developed in 1987 and designated as a Master Cell Bank in 1998. Producers of biologicals and national control authorities can obtain cultures of these Vero cells (free of charge), as well as additional information, from WHO.

At it's meeting in February 2003, the Expert Committee on Biological Standardization was informed of the outcome of a meeting of a WHO Monitoring Group on Cell Banks held in Potters Bar, UK in October 2002 (2). The Monitoring Group noted that significant changes in regulatory expectations and technological advances have occurred in the requirements of cell bank operation and testing since the development of the WHO Vero bank 10-87 in 1987 and its designation as a Master Cell Bank in 1998. The Committee endorsed a recommendation from the Monitoring Group that the 10-87 bank should not be considered as a Master Cell Bank for direct use in manufacturing processes. Rather, the 10-87 bank should be regarded as a Cell Seed qualified by scientific analytical consensus from which Master Cell Banks (MCBs) may be established for thorough re-qualification. The Committee noted (3) that it would be necessary to revise the Requirements for the use of animal cells as in vitro substrates for the production of biologicals (WHO TRS 878, 1998) to accommodate this change.

Manufacturers testing regimes for Master Cell Banks derived from the WHO Vero 10-87 Cell Seed will need to expand on the tests used to establish the WHO Vero 10-87 bank to include techniques such as product enhanced reverse transcriptase (PERT) assays (2). Furthermore, manufacturers should maintain their awareness of current developments in the field of adventitious agents and ensure that safety testing data on banks of cells used in manufacturing processes are regularly reviewed and updated where appropriate.

The redesignation of the WHO Vero bank 10-87 as a Cell Seed may lead to investigations into the use of cells for manufacturing processes at higher population doublings than has previously been recommended. The potential for increased tumourogenicity at higher population doublings, amongst other issues, must therefore be considered (2). This assessment of tumourigenicity should take into account the variation that may occur in assessment of population doublings (both between and within laboratories), the potential for variability of *in vivo* tumourogenicity tests and the variation

Adopted by the 54th meeting of the WHO Expert Committee on Biological Standardization, 17-21 November 2003. A definitive version of this document, which will differ from this version in editorial but not scientific details, will be published in the WHO Technical Report Series.

between different cell culture processes. The establishment of arbitrary passage limits for the use of cells in a manufacturing process may be of lesser significance than careful process validation and testing of cells passaged beyond the process limits.

The amendments to the 1998 Requirements are in the section titled "General Considerations" and are given below:

General Considerations

Continuous-cell-line substrates

The last paragraph on page 23 of WHO Technical Report Series number 878 currently reads:

"The WHO master cell bank of Vero cells is stored at the European Collection of Animal Cell Cultures (ECACC), Porton Down, England and the American Type Culture Collection (ATCC), Rockville, MD, USA. Producers of biologicals and national control authorities can obtain cultures of these Vero cells (free of charge), as well as additional background information, from Biologicals, World Health Organization, 1211 Geneva 27, Switzerland."

This paragraph is now changed to read:

"The WHO 10-87 cell bank of Vero cells is stored at the European Collection of Animal Cell Cultures (ECACC), Porton Down, England and the American Type Culture Collection (ATCC), Rockville, MD, USA. This cell bank should be regarded as a Cell Seed qualified by scientific analytical consensus from which Master Cell Banks (MCBs) may be established for thorough re-qualification. Producers of biologicals and national control authorities can obtain cultures of these Vero cells (free of charge), as well as additional background information, from Quality Assurance and Safety of Biologicals, World Health Organization, 1211 Geneva 27, Switzerland."

References

1. Requirements for the use of animal cells as *in vitro* substrates for the production of biologicals. WHO Technical Report Series, 878, 1998, Annex 1.
2. Report of the WHO Monitoring Group on Cell Banks, 16-17 October 2002.
3. Expert Committee on Biological Standardization, Fifty-second report, in preparation.