Annex 6

Requirements for rabies vaccine for veterinary use (Requirements for Biological Substances No. 29, amendment 1992)
The WHO Expert Committee on Rabies, which met in 1991 in Geneva, issued a recommendation to manufacturers and national control authorities to the effect of increasing the minimum potency of suckling-mouse brain inactivated rabies vaccine for veterinary use (1). Furthermore, since the Requirements for Rabies Vaccine for Veterinary Use were published in 1981 (2), new international reference materials for rabies vaccine and rabies immunoglobulin have been established, and the revised Requirements for Biological Substances No.1 (General Requirements for Manufacturing Establishments and Control Laboratories) have been replaced with quality assurance guidelines for national authorities (3) and recommended good manufacturing practices for biological products (4). These changes have necessitated the following amendments to the Requirements for Rabies Vaccine for Veterinary Use.

General considerations (pages 99–100)

Replace the part of the fourth paragraph on page 99 beginning "A common reference preparation . . ." and ending on the first line of page 100 " . . . and the potency of the newer types of vaccine." by the following:

"The fifth International Standard for Rabies Vaccine was established by the WHO Expert Committee on Biological Standardization in 1991, with a potency of 16 International Units of Rabies Vaccine per ampoule. Recent research has indicated that the glycoprotein and ribonucleoprotein components of inactivated rabies vaccines play an important role in conferring protection. For this reason, the Committee also assigned 10 International Units of Rabies Virus PM-Glycoprotein and 135 International Units of Rabies Virus PM-Ribonucleoprotein to the contents of each ampoule of the International Standard. It is recognized, however, that these components might differ antigenically in the different virus strains used for vaccine production; the International Standard may therefore be inappropriate for the estimation of glycoprotein and ribonucleoprotein components of vaccines not derived from the Pitman-Moore (PM) strain.

It is hoped that potency assays of inactivated rabies vaccines in animals will eventually be replaced by determinations of antigen content. However, the potency estimation in these Requirements is still based on assays using intracerebral challenge of previously immunized mice (the so-called NIH
test) since consensus has not yet been reached on suitable tests based on antigenic content."

**Definitions (pages 101–102)**

*Replace* the whole of section 1.3 (International Reference Preparation and International Standard) by the following:

**1.3 International reference materials**

"The fifth International Standard for Rabies Vaccine and the first International Standard for Rabies Immunoglobulin are in the custody of the International Laboratory for Biological Standards, State Serum Institute, Copenhagen, Denmark. Samples are distributed free of charge, on request, to national control laboratories. The international reference materials are intended for the calibration of national reference materials for use in the manufacture and laboratory control of rabies antibody preparations and vaccines."

**Good manufacturing practices**

On pages 103, 114, 117 and 118, *replace* every reference to the revised Requirements for Biological Substances No.1 (General Requirements for Manufacturing Establishments and Control Laboratories) by references to Good Manufacturing Practices for Pharmaceutical Products and Good Manufacturing Practices for Biological Products, and add appropriate bibliographic details to the reference list (see 4 and 5 below).

**Control tests on final product**

5.4.1 *Potency test of inactivated vaccines (page 116)*

The first two paragraphs remain unchanged. *Replace* the rest of the section, beginning in large print "The potency of each filling lot ..." and finishing in small print "... of the reference preparation." by the following:

"The estimated potency of each filling lot shall not be inferior to that of a reference vaccine that has been shown to be efficacious in all species of animal for which the vaccine is intended. The minimum potency shall be approved by the national control authority.

The mean potency should not be less than 1.0 IU per single dose. Reproducibility of the results of tests depends in part on the strain of rabies virus and the consistency of the virus challenge dose used. The strain of mouse may also affect reproducibility.

The relative potency of the reference vaccine included in each test shall have been determined in International Units by comparison with the International Standard for Rabies Vaccine. The potency of the test vaccine in International Units shall then be determined by comparison with the reference vaccine.

When the NIH test is used, it is advisable to use seven vaccine dilutions, with a logarithmic dilution ratio of 0.7 and ten mice per dilution."
Replace the whole of the small-print section “The test for potency ... to show consistency of production.” by the following:

“The test for potency (see Part A, section 5.4) made on vaccine samples stored at 37 °C for two weeks (inactivated vaccines) or one week (live vaccines) is suitable. In order to pass the test, the vaccine should retain the minimum potency, as defined in Part A, section 5.4.

In some countries, each lot of vaccine must be subjected to the stability test, whereas in others the test is required only to show consistency of production before application for a licence.”

National control requirements (page 119)

Replace the first paragraph of section 1 (“The general requirements for control laboratories ... shall apply.”) by “The Guidelines for National Authorities on Quality Assurance for Biological Products shall apply.” and add appropriate bibliographic details to the reference list (see 3 below).

References


