Annex 4

Requirements for rabies vaccine for human use
(Requirements for Biological Substances No. 22, amendment 1992)

Since the Requirements for Rabies Vaccine for Human Use were published in 1980 (1), several developments have occurred. In 1991, the WHO Expert Committee on Rabies issued a recommendation to manufacturers to the effect of increasing the minimum potency of inactivated rabies vaccines derived from suckling-mouse brain tissue for human use (2). In the same year, the revised Requirements for Biological Substances No.1 (General Requirements for Manufacturing Establishments and Control Laboratories) were replaced by the WHO Expert Committee on Biological Standardization with quality assurance guidelines for national authorities (3) and recommended good manufacturing practices for biological products (4).

Furthermore, new international reference materials were established by the WHO Expert Committee on Biological Standardization in 1991.

It is thus appropriate to modify as follows the existing Requirements for Rabies Vaccine for Human Use.

General considerations (page 58)

Replace the paragraph “The International Reference Preparation of Rabies Vaccine . . . 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 (page 60)

*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 61, 62, 76, 79 and 82, *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 *Potency test of vaccine in final containers (page 77)*

*Replace* the whole of the small-print section “Reproducibility of the test... testing of successive batches.” by the following:

"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 reference vaccine included in each test shall be calibrated in International Units by comparison with the International Standard for Rabies Vaccine. The potency of the test vaccine in International Units shall be determined by comparing its activity with that of the reference vaccine in the NIH test (10). The confidence limits of the assay shall be approved by the national control authority.

The estimated geometric mean potency should be based on two or more tests and should be at least:

- 2.5 IU per single human dose for purified cell-culture vaccines given in a two- or three-dose pre-exposure schedule, or in a post-exposure schedule of up to six doses;
- 1.3 IU per single human dose for suckling-mouse brain vaccines."

As a result of the replacement of the international reference material for rabies vaccine, footnote number 4 disappears from the bottom of page 77.
5.5 Stability test for freeze-dried vaccine (page 78)

*Replace* the whole of the small-print section “In some countries . . . to show consistency of production.” by the following:

“The test for potency (see Part A, section 5.4) made on vaccine samples stored for four weeks at 37°C is suitable. In order to pass the test the lot 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.

In some countries, stability is ascertained by testing samples throughout the shelf-life of the vaccine.”

5.8 Test for pyrogenicity (page 78)

*Replace* the existing text with: “Each final lot shall be tested for pyrogenic substances. The test shall be approved by the national control authority.”

National control requirements (page 80)

*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


