WHO Technical Report Series, No. 840, 1994

Annex 5
Requirements for rabies vaccine (inactivated) for human use produced in continuous cell lines
(Requirements for Biological Substances No. 40, amendment 1992)

To be consistent with the amended Requirements for Rabies Vaccine for Human Use (*1*), the Requirements for Rabies Vaccine (Inactivated) for Human Use Produced in Continuous Cell Lines (*2*) should be modified as follows.

General considerations (page 168)

Insert the following text between the third paragraph, ending "... international requirements for these vaccines." and the fourth paragraph, beginning "Each of the following sections . . .":

"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 169–170)

Replace the first two paragraphs of section 1.3 (International Standards), beginning "The International Standard for Rabies Vaccine . . ." and finishing on the ninth line of page 170 ". . . a potency of 59 IU per ampoule (*8*, p.17).", 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 171, 172, 181, 183 and 184, *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 *3* and *4* below).

Control tests on final product

6.5 ***Potency test of vaccine in final containers (page 182)***

Replace the whole small-print section "Reproducibility of the test . . . found in two or more tests." 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 (*12*). 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."

6.6 ***Stability test (page 183)***

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 6.5) 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 6.5.

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."

National control requirements (page 185)

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 5 below).

References

1. Requirements for Rabies Vaccine for Human Use (Requirements for Biological Substances No. 22), Amendment 1992. In: *WHO Expert Committee on Biological Standardization. Forty-third Report.* Geneva, World Health Organization, 1994, Annex 4 (WHO Technical Report Series, No. 840).
2. Requirements for Rabies Vaccine (Inactivated) for Human Use Produced in Continuous Cell Lines (Requirements for Biological Substances No. 40). In: *WHO Expert Committee on Biological Standardization. Thirty-seventh Report.* Geneva, World Health Organization, 1987, Annex 9 (WHO Technical Report Series, No. 760).
3. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second Report.* Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).
4. Good manufacturing practices for biological products. In: *WHO Expert Committee on Biological Standardization. Forty-second Report.* Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 822).
5. Guidelines for national authorities on quality assurance for biological products. In: *WHO Expert Committee on Biological Standardization. Forty-second Report.* Geneva, World Health Organization, 1992, Annex 2 (WHO Technical Report Series, No. 822).

37. Requirements for Continuous Cell Lines Used for Biologicals Production
    Adopted 1985, TRS **745** (1987)

38. Requirements for Mumps Vaccine (Live)
    Adopted 1986, TRS **760** (1987)
    Replaced by Requirements No. 47

39. Requirements for Hepatitis B Vaccines Made by Recombinant DNA Techniques in Yeast
    Adopted 1986, TRS **760** (1987)
    Replaced by Requirements No. 45

40. Requirements for Rabies Vaccine (Inactivated) for Human Use Produced in Continuous Cell Lines
    Adopted 1986, TRS **760** (1987)
    Amendment 1992, TRS **840** (1994)

41. Requirements for Human Interferons Made by Recombinant DNA Techniques
    Adopted 1987, TRS **771** (1988)

42. Requirements for Human Interferons Prepared from Lymphoblastoid Cells
    Adopted 1988, TRS **786** (1989)

43. Requirements for Japanese Encephalitis Vaccine (Inactivated) for Human Use
    Adopted 1987, TRS **771** (1988)

45. Requirements for Hepatitis B Vaccines Made by Recombinant DNA Techniques
    Adopted 1988, TRS **786** (1989)

46. Requirements for *Haemophilus* Type b Conjugate Vaccines
    Adopted 1990, TRS **814** (1991)

47. Requirements for Measles, Mumps and Rubella Vaccines and Combined Vaccine (Live)
    Adopted 1992, TRS **840** (1994)

48. Requirements for Vi Polysaccharide Typhoid Vaccine
    Adopted 1992, TRS **840** (1994)

Requirements for Immunoassay Kits [unnumbered]
    Adopted 1980, TRS **658** (1981)

Other documents

Recommendations for the assessment of binding-assay systems (including immunoassay and receptor assay systems) for human hormones and their binding proteins (A guide to the formulation of requirements for reagents and assay kits for the above assays and notes on cytochemical bioassay systems)
TRS **565** (1975)

Development of national assay services for hormones and other substances in community health care
TRS **565** (1975)

Report of a WHO Working Group on the Standardization of Human Blood Products and Related Substances
TRS **610** (1977)

Guidelines for quality assessment of antitumour antibiotics
TRS **658** (1981)

The national control of vaccines and sera
TRS **658** (1981)
Replaced by "Guidelines for national authorities on quality assurance for biological products", TRS **822** (1992)

Procedure for approval by WHO of yellow fever vaccines in connexion with the issue of international vaccination certificates
TRS **658** (1981)

A review of tests on virus vaccines
TRS **673** (1982)

Standardization of interferons (reports of WHO informal consultations)
TRS **687** (1983)
TRS **725** (1985)
TRS **771** (1988)

Production and testing of the WHO yellow fever virus primary seed lot 213-77 and reference batch 168-73
TRS **745** (1987)

Report of a WHO Meeting on Hepatitis B Vaccines Produced by Recombinant DNA Techniques
TRS **760** (1987)

Procedure for evaluating the acceptability in principle of vaccines proposed to United Nations agencies for use in immunization programmes, revised 1988
TRS **786** (1989)

Guidelines for the preparation, characterization and establishment of international and other standards and reference reagents for biological substances, revised 1989
TRS **800** (1990)

Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology
TRS **814** (1991)

Good manufacturing practices for biological products
TRS **822** (1992)

Guidelines for national authorities on quality assurance for biological products
TRS **822** (1992)

Guidelines for assuring the quality of monoclonal antibodies for use in humans
TRS **822** (1992)

Laboratories approved by WHO for the production of yellow fever vaccine, revised 1991
TRS **822** (1992)