Report

Discussion on WHO Requirements for Rabies vaccine for human use

World Health Organization
Geneva, Switzerland

4-5 May 2004
Introduction and background

Dr David Wood, coordinator of the Quality Assurance and Safety of Biologicals team welcomed participants to the World Health Organization and outlined the objectives of the meeting. He reminded the group that the WHO, through considerable international consultation, develops recommendations and guidelines on the production and control of vaccines and other biologicals of significance, and these form the basis for assuring the acceptability of products globally. For rabies vaccine, the last revision was in 1980 (Requirements for rabies vaccine for human use, WHO TRS 658, annex 2). In addition, WHO Requirements for rabies vaccine (inactivated) for human use produced in continuous cell lines (TRS 760) were published in 1987. An amendment which documented the introduction of new reference materials was published in the TRS 840, annex 5, in 1994. Since that time, significant advances in the production and control of rabies vaccines have been made.

A meeting of a working group on potency assays for rabies vaccines was convened at the WHO, on 20 May 2003 to review the current approach in potency testing and the recent data generated on the in vitro assays. The report of this meeting is available on the following web site www.who.int/biologicals.

A drafting group was set up to initiate the revision of the current requirements. The drafting group consisted of the experts in production and control of rabies vaccines for human use and involved regulators as well (list of participants in the annex). Dr Robin Levis and Dr Morag Ferguson were appointed chair and rapporteur, respectively.

This drafting group had been convened to review the current requirements for rabies vaccines for human use (1-4) and to propose revisions. These draft recommendations would go through a global consultation process involving vaccine industry, National Regulatory Authorities (NRA), Academia, public health authorities, in 2004 and 2005. The final draft would then be submitted to the Expert Committee on Biological Standardisation in the autumn of 2005, for adoption.

Dr Ivana Knezevic outlined the method of work which was to focus discussion on critical issues and to make proposals for revision. The issues identified as critical are the scope of the document, substrates for vaccine production; the inactivation process; the test for effective inactivation following a recent problem with one product; potency and the use of in vitro assays for determination of the antigen content; stability tests and the value of accelerated degradation test; NRA requirements.

A review of the current manufacturing practice is essential at the beginning of the revision since this reflects the changes to be considered in the document. The proposals for recommendations should also take into account the regulatory perspective and the problems seen in quality control. A revised draft based on the Requirements for Rabies Vaccine (Inactivated) for Human Use Produced in Continuous Cell Lines published in WHO Technical Report Series 760 (1) would be produced. Any issues from TRS 658 (2) and TRS 840 (3, 4) not considered in TRS 760, such as vaccines produced in diploid cells, primary cell lines and embryonated eggs would be incorporated into the revised version. The revision should also address reference to issues raised in the requirements
for cell substrates which were published in TRS 878 (5). The group were reminded that any proposed changes to the requirements should be supported by data.

The group were informed that additional background information was available in the report of Expert Committee on Rabies Vaccine published in TRS 824 in 1994 which deals with all issues related to rabies disease, such as immunisation schedules, surveillance, epidemiology of rabies etc. There were also a WHO position paper and the draft report of a meeting held in May 2003 to discuss potency tests.

**Industry perspective**

Dr Alain Sabouraud gave the Aventis Pasteur (AvP) perspective on the requirements for rabies vaccine. He requested that there be harmonization between the European Pharmacopoeia (EP) and WHO requirements with respect to the test for complete inactivation as manufacturers have to undertake different tests for batches destined for different markets. Test for inactivation should include a direct test in mice and an indirect test by amplification on cell substrates. The EP permits the use of immunofluorescence for the detection of virus in cell culture whereas the WHO requirements require test in mice. In addition, virus titration over the first detoxification hours would give the expected slope of inactivation curve. Such information is not currently required by WHO but Dr Sabouraud suggested that this would give added information as to the consistency of production and added assurance of safety.

The inclusion of trypsinisation of cells, as required by the EP, is another difference in the tests required by WHO and the EP. Dr Sabouraud questioned whether trypsinisation improves sensitivity of the assay in practice as anticipated. He reported that AvP had undertaken studies on the limits of detection through the examination of various parameters. Their conclusions were that there was no significant difference in the sensitivity of the assay, a) by the use of immunofluorescence and inoculation of mice and b) when cells were trypsinised on day 7 (EP method) or not (WHO method). However, Vero cells were more sensitive than MRC5 cells. Dr Sabouraud indicated that AvP was willing to supply data to support any changes to WHO recommendations.

In a recent amplification test for effective inactivation performed retrospectively for regulatory purpose on a production batch, two mice unexpectedly died of rabies on day 14. It was unclear whether this was caused by residual infectivity as a consequence of ineffective inactivation or cross contamination by live virus. Dr Sabouraud proposed that analysis of the kinetics of inactivation (slope), which is product- and process-specific, be introduced on a routine basis to monitor virus inactivation effectiveness.

Dr Sabouraud indicated that AvP had been evaluating an EIA for potency assays. Although antigen content determined by EIA gave a good correlation with that obtained in single radial immunodiffusion tests (SRD), it gave a poor correlation with potencies determined in the NIH test.

Dr Sabouraud queried the continued inclusion of the accelerated degradation stability, which requires testing of vaccines after storage at 37°C for 4 weeks to be performed on every batch. From AvP experience, the potency of the vaccine when stored at 37°C is consistently around 10% lower than that of the vaccine at 5°C. He commented that there has been no batch failure as a result of stability testing using the NIH test. Removal of
this test in routine use, following satisfactory performance of validation studies for new products, would be an opportunity for the reduction in animal usage. Consideration should also be given to the introduction of a single dose mouse protection test such as described in the EP monograph for human vaccines. Such a test is likely to be acceptable for vaccines which are routinely of 7-8 IU/dose but not suitable for vaccines containing 3-4 IU which are close to the minimum requirement of 2.5 IU/dose.

Dr Reiner from Chiron queried whether it would be possible to delete mycoplasma testing at some stages of production, e.g., on the harvest or after inactivation or whether it was sufficient to undertake on the control cells. The group commented that this is classical approach for all vaccines. The inclusion of a filtration step for the bulk was discussed and he commented that there is a loss of activity at 0.22µ but not at 0.45µ. This could then not be considered as a sterilization step. It would also require validation of aseptic process. This should be considered further with perhaps a general comment but no specification.

Regulatory perspective

Dr Correa de Moura described the testing performed for batch release by the NCL in Brazil. Currently there is no rabies vaccine production in Brazil and the Vero cell vaccine from Aventis is now being purchased in bulk with only labelling and packaging being undertaken. Suckling mouse brain vaccine is no more produced in Brazil.

Dr Levis agreed that the issues already raised were relevant and that the unification of requirements would be helpful.

Dr Ferguson listed a series of issues, some of which had already been raised by other participants:

- A single set of requirements for all cell culture derived vaccines, HDCS, continuous cell lines and PCEC
- Deletion of requirements for sheep brain vaccine
- TSE issues where bovine material is used in medium
- The quality of human albumin used in production
- The use of preservatives is not addressed fully in the current requirements
- Adjuvant may affect the potency obtained in *in vitro* assays
- Different methods of purification
- Update assays for residual infectious virus
- Purity / limit of residual DNA
- Pyrogenicity – is the use of LAL test acceptable
- Update reference to IS and consider ongoing suitability of RAV as the IS.
- Effect of strain difference between vaccine and the IS with respect to potency and antigen content.
- *In vitro* potency tests and suitability for application to stability studies

Dr Tahlan from the Indian NCL listed his concerns about the current requirements. He informed the group that there is growing concern about the usage of sheep brain rabies vaccine in India, and the efforts are afoot for its replacement by newer rabies vaccines
in very near future. Large quantities of cell culture vaccine produced in India are now available so this policy is likely to be enforced.

Table 1 Vaccines produced in India

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Cell substrate</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Chiron India</td>
<td>PCEC</td>
<td>Same as Chiron Germany</td>
</tr>
<tr>
<td>2 Cadilla</td>
<td>Purified duck embryo</td>
<td>Berna technology transfer</td>
</tr>
<tr>
<td>3 Serum Institute of India, Pune, India</td>
<td>MRC5</td>
<td>Liquid &amp; Lyophilized preparation Bioport, Michigan USA technology</td>
</tr>
<tr>
<td>4 Human Biological Institute, Ooty, TN, India</td>
<td>Vero cell</td>
<td>Indigenous Technology</td>
</tr>
<tr>
<td>5 Pasteur Institute of India, Coonoor</td>
<td>Vero cell</td>
<td>Indigenous Technology</td>
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India produces approximately 10 million doses of tissue culture rabies vaccine each year. The Serum Institute of India, Pune, produces gel adsorbed liquid and lyophilized rabies vaccine using MRC-5 cells. Both of these products meet the accelerated thermal stability test requirements. and there is now production capacity within India of cell culture or PDEV to meet this requirement.

The vaccine produced by Serum Institute of India which is manufactured on MRC5 cells, is an aluminium adjuvanted vaccine in liquid form and they also produce lyophilised vaccine using the same substrate. Dr Tahlan stated that stability of liquid preparations may differ in comparison with the lyophilised vaccines, but he pointed that this fact is well known and scientifically acceptable. Group recommended that each manufacturer will have to demonstrate adequate stability at the recommended storage temperature and when stored at other temperatures as part of accelerated degradation studies. Dr Knezevic indicated that new WHO guidelines for stability testing of vaccines are under development and general principles on thermal stability testing in this new guidance may help to improve current test for rabies vaccines.

Dr Tahlan also reminded the group that the specification for residual DNA level and the use of SPF eggs should be made consistent with those listed in the requirements for cell substrates (TRS 878). He also queried whether the same EIA could be used for different vaccines and also the same reference.

Dr Gibert from AFSSAPS indicated that their tests for antigen content on vaccines produced by AvP in MRC5 and Vero cells demonstrated good consistency. They would prefer an in vitro potency test but consideration needs to be given to the availability of reference vaccines and monoclonal antibodies. There is also a need for such assays to be applied to stability testing.

Use of rabies vaccines
The group discussed available data on the use of rabies vaccines. The information provided at the meeting (table 7, RIMSA 13/INF/2 Sp, p.47, Reports of the countries to the VII REDIPRA, 2000 and IX REDIPRA, 2002) indicates that 5,817,413 doses of Fuenzalida type vaccine and 816,814 doses of cell culture type vaccine were produced in Latin America in 2000-2001. In Asian countries rabies vaccines are produced in suckling mouse brain, sheep and goat brain.

An issue which was mentioned outside of the meeting was the availability of virus strains suitable for vaccine production. In the TRS 658 there is a footnote that WHO could provide such strain. The availability of rabies virus for production of vaccines should be further explored.

RECOMMENDATIONS ON THE SCOPE OF THE USE OF RABIES VACCINES

1. The production and use of vaccines produced in neural tissues (sheep, goat brain etc) should be discontinued and this statement should determine the scope of the recommendations for production and control of rabies vaccines.

2. A survey should be undertaken to obtain data on the types of vaccines (virus strain and substrate used for production) in current use. Detailed information on the type of rabies vaccines, number of doses produced per year and number of doses applied per year in different countries will be useful for the revision of the recommendations. Information concerning the major obstacle in switching to cell culture production such as difficulty in sourcing a suitable strain of virus for production, the cost of production in cell culture and subsequent increase of the price of the vaccine should also be investigated.

Discussion on potency testing

The group considered the potency testing of rabies vaccines. Dr Grachev reminded the group of the inherent variability of the NIH mouse protection test and the variation obtained in tests on the same batch of vaccine. He also queried the current minimum potency requirement of 2.5IU/dose and whether that could be reduced. However, Dr Ferguson reminded the group that this value was based on the potency of the vaccine batch demonstrated to be efficacious in the trials of HDCS vaccines undertaken among people who were bitten by proven rabid animals in Iran in the 1970s.

Dr Grachev indicated his preference for in vivo assays as it has been shown to be related to protection and over the past 15-20 years, vaccines which pass this test have been efficacious. However, there has been no demonstration of a relationship between EIA and efficacy. Dr Grachev also questioned whether the current 5th International Standard is applicable and whether this standard is still appropriate for use with all current vaccines.

The group reviewed the conclusion of the meeting held to discuss potency tests of rabies vaccines on 20 May 2003 that there is no correlation between the NIH and EIA test data. Such a correlation was required by ECBS 10 years ago when it rejected proposals for the introduction of tests for glycoprotein antigen content as a replacement for the NIH test in vaccine of proven consistent production.
Dr Sabouraud reminded the group that in Europe, every batch is tested in the NIH test by the manufacturer. They are required to perform 2 tests for batch destined for the US and these batches pass if the geometric mean is >2.5 IU/dose. AFSSAPS tests 1 in 10 batches in the NIH test but all batches by EIA. CBER test 25-33% of vaccines received for lot release following review of the protocols. Some batches from each manufacturer were tested by NIH each year.

Dr Sabouraud then proposed that a single dose mouse protection test be recommended on vaccines for which the parameters of the NIH tests have been established with well-established vaccines as this was now an option in the EP monograph. Such a test is not performed by either AvP or Chiron on vaccines for human use but it is used by manufacturers and control laboratories on rabies vaccines for veterinary use. A single dilution test has been introduced for diphtheria and tetanus vaccines but such tests lose precision. Before limit can be established, laboratories need to do a large number of full tests before implementation.

None of the group members was aware of the data presented to Group 15 in support of this change to the EP monograph for human rabies vaccine and it was agreed that EDQM should be asked for the data presented in support of the change to the EP. It was agreed that the manufacturers should investigate use of a single dose test.

The group agreed that assays for glycoprotein antigen content demonstrate consistency of production. However, a correlation with NIH test results has not been shown in the majority of studies undertaken (6-15). The group agreed that in vitro assays could complement the NIH test undertaken by manufacturers and that such tests could also be performed by NRAs. It was suggested that EIA is a measurement of consistency of production and could be used along with the NIH test for a period of time. After a review of data generated from tests in parallel, the deletion of the NIH test could be considered for an individual vaccine.

The group then considered available reagents and whether monoclonal antibodies can differentiate between antigenic but not immunogenic vaccines. Reagents which react only with conformational epitopes found on immunogenic antigen are available and include monoclonal antibodies D1 from Institute Pasteur.

This antibody is utilised in the assay performed routinely by AFSSAPS. In this assay the same antibody is used coating plates and detection of bound antigen. AFSSAPS had data demonstrating the consistency of a large number of batches of AvP vaccines against several reference preparations. There was a better correlation with Vero cell vaccine but it was pointed out that this vaccine is formulated on the basis of in vitro tests. In the case of Vero cell vaccine (not chromatographically purified) the glycoprotein antigen content measured by ELISA and expressed in IU/ml, were lower than expected on the basis of NIH potency data, also expressed in IU/ml.

Dr Sabouraud presented data on EIA studies performed by Aventis Pasteur on both HDCV and Vero vaccines. These assays involved the use of polyclonal anti-glycoprotein sera from NIH or NIBSC and monoclonal antibodies originally from the Wistar Institute – 507-1, 1112-1, 1105-3, TW17 from Chiron and D1-25 from Institute Pasteur. The assay was a classical EIA and similar results were obtained with all of the antibodies with all monoclonal antibodies. The assay involved coating plates with
monoclonal antibody and the use of a polyclonal antibody as detector. Dr Reiner commented that this is the reverse of that undertaken by Chiron which involves coating plates with polyclonal antibody and the use of a monoclonal antibody as detector.

AvP have demonstrated that vaccine batches stored at 40, 50 and 60°C indicated increasing loss of potency when assayed against the same batch stored at 2-8°C. Degradation had also been demonstrated in assays with the Institute Pasteur antibody and these increases with temperature. The samples have not been tested in NIH tests. The results of SRD assays on HDCV vaccine batches correlated with EIA test results. However, there was no correlation between NIH and SRD or EIA test results although slope is positive.

Dr Sabouraud indicated that Aventis preferred to have antibodies against different sites and that all reagents were monoclonal antibodies and therefore more readily available over the long-term. Participants agreed that antibodies directed against either antigenic site 3 or site 2 of the viral glycoprotein should be good for an assay.

Dr Kumar presented the results of studies undertaken at CBER on batches of vaccine assayed against either PISRAV (the US reference) and Chiron monoclonal antibodies. Reconstituted PISRAV stored at elevated temperatures was assayed by EIA and in NIH tests and examined by electron microscopy to investigate the integrity of the virus. EIA showed reduction in EIA responses. Similar results were obtained with other vaccines. Electron microscopy of RCC5 which is a batch of Chiron vaccine revealed clumped viral particles at higher temperatures. TW1 recognises an epitope not as sensitive to heating as TW17.

The group reviewed the availability of monoclonal antibodies used in the assays so far. TW1 and TW17 are available via NIBSC, D1 is available for purchase from Dr Tordo at the Institute Pasteur. Aventis have a Material Transfer Agreement for this antibody and will investigate whether they could supply the antibody, but not cells, to other laboratories.

**Suggested way forward**

Multiple studies have demonstrated that it is unlikely that a correlation between NIH and EIA potencies can ever be demonstrated and it was suggested that a list of studies already performed be compiled and presented to ECBS. Data from NIBSC, AFSSAPS, Aventis, Chiron and CBER would be included in this database. Dr Ferguson agreed to prepare the template for key parameters of the assays undertaken such as the reference material used, the upper and lower limits, mean correlation, the monoclonal antibodies used for detection and the epitopes recognised by the antibodies. Dr Knezevic also proposed send the report of this meeting to NRAs to determine their views and find out the extent of studies undertaken and available data.

Dr Levis indicate that she had funds to organise a small meeting to discuss with experts on test validation what data the FDA regulators would expect when submission is made, on the assumption that no correlation between NIH and EIA test potency is found. The CFR says tests must be as good as or better than that in current use.
Dr Wood also suggested that the EMEA Vaccine Evaluation Group (Chairman Dr Roland Dobbelaer) be asked what evidence they would expect to see before accepting an in vitro assay as a replacement for the NIH test so that the expectations of regulators were known. Dr Ferguson subsequently discussed this suggestion with Dr Minor at NIBSC and he recommended that proposals should be presented to the EMEA VEG group for comment rather than seeking their suggestions.

Dr Bourhy told the group that there is a call for EU framework 7 grants which would facilitate clinical trials on batches tested in the clinic if the correlation of EIA potency to clinical efficacy was seen as an appropriate approach. None of the group indicated a willingness to take this forward. However, it was agreed that it would be worth investigating there are any other projects on vaccines underway.

**Recommendations of the meeting concerning potency**

1. There is enough evidence that the correlation between in vivo (NIH) and in vitro tests (SRD, EIA) cannot be established for all vaccines (DEFRA project, AFSSAPS data, data from manufacturers, Aventis and Chiron, should also be provided to support it).
2. Antigen content measurement is a good measure of consistency of production and is also a good test for regulators to test rabies vaccines. Therefore, it should be proposed for adoption.
3. Action to be taken: Data from Aventis, Chiron, NIBSC, AFSSAPS, CBER to be analysed in terms of vaccines tested, tests performed, the parameters monitored and references and reagents used. Morag Ferguson to prepare a template to be filled in and data collected. Statistical analysis should also be done. If data sufficient to demonstrate that antigen content measurement provides relevant information, feasibility study as considered before may not to be done. Also, data that EDQM used to require this test to be done on every lot should be considered.
4. If any clinical trial is now ongoing or planned, this opportunity should be taken to test correlation between antigen content and efficacy (measured by immunogenicity) in this trial.
5. With respect to NIH test, this will stay potency assay. A single dilution NIH test may be a good option for the time being. However, further investigation is needed to define how this test could be performed and whether periodical performance of full NIH test would give additional value to it. Data from manufacturers (Aventis) to be reviewed.
6. Reference reagents should be further discussed.

**Key issues to be addressed in the updated requirements**

The group agreed that the requirements for rabies vaccines produced in continuous cells lines, TRS 760, would serve as the basis for the updated requirements which would become recommendations in line with WHO current practice. They reviewed this document in detail and comments on each section will be annotated on an in an accompanying document.
Dr Knezevic told the group that the introduction to the requirements in TRS 760 would be updated to explain the merger of the 2 sets of requirements and the addition of sections on the additional substrates. This section would also include a summary of the safety and efficacy of current vaccines and adverse events reported and comments on why freeze dried vaccines are preferable to liquid vaccines. A statement about potency of vaccines used for intradermal immunization (e.g., vaccines of higher potency as recommended by the Expert Committee on Rabies) would also be included and a re-emphasis that studies to demonstrate efficacy must be undertaken for each vaccine. The loss of potency which could be detected by an in vitro and in vivo test should also be discussed.

The updated section on standards published in TRS 840 would be incorporated. Relevant sections of the Requirements for cell substrates TRS 878 would be included or referenced, as would reference to the recommendations on TSE.

Other sections which the group indicated required to be updated included the definition of ‘fixed’ virus; state of the art methods used for the characterization of rabies vaccines; updating the tests for Mycobacterium Tuberculosis; tests on virus seeds for adventitious agents; the identity test of the production cell line; specifications for residual DNA updated in line with the cell substrates requirements; clarification of the concentration of BSA as an indicator of animal serum.

The major discussion focussed on the sections for inactivation and tests for effective inactivation and the agreed outcomes are documented in the updated draft.

**Summary of major proposed revisions**

**The scope of the Recommendations**

The scope should include vaccines produced in cell cultures, primary (hamster and chick embryo), human and monkey diploid and continuous cell lines and vaccines containing inactivated virus purified from duck embryos. As the production of vaccines in neural tissue is likely to continue for a further 2-3 years, the group suggested that the requirements for rabies vaccines for human use, TRS 658 should not be discontinued when the revised requirements for rabies vaccine are accepted but remain valid for the production of mouse brain vaccines of the Fuenzalida type for a defined period (e.g., 3 years).

**Inactivation procedure**

1. Inactivation should be done after clarification and purification, within 24 hours to avoid aggregation of viruses.
2. The total inactivation time used must be demonstrated through the kinetic of inactivation, and the period should be at least double the period required to inactivate the virus completely.
3. As a part of validation of the inactivation process, virus samples taken at appropriate times, shall be inoculated immediately into the sensitive substrate (e.g., mice, cell cultures), to determine inactivation curve. This could provide information on the reproducibility of the inactivation process.
**Test for effective inactivation**

1. Direct inoculation test to be deleted. This test is not sensitive enough and the recommendation is made to use virus amplification test only.
2. In the virus amplification test: The rabies virus amplification test (5) shall be performed in the cell culture used for vaccine production or a type of cell line of greater sensitivity which has been demonstrated, to test for the presence of live virus.

Small print:
Manufacturers are encouraged to use cells of great sensitivity for the tested virus (such as BHK-21, Vero). Cell line should be approved by the NRA.

Consideration should be given as to whether the amplification test could be deleted if a demonstration of inactivation kinetics on every batch is undertaken by the manufacturer.

The inclusion of a filtration step for the bulk should be considered further with perhaps a general comment but no specification.

**Innocuity test**

Proposal made to delete this test in the recommendations for rabies as well as in all other recommendations for production and control of vaccines as there is no evidence that this adds to the safety of rabies vaccines under consideration in these requirements.

**Stability data**

Proposal made to delete accelerated degradation test (at 37°C) or to do it periodically. The importance of stability study to support shelf life should be mentioned.

**National Regulatory Recommendation and Summary protocol**

These will be further discussed when there is a more mature draft of recommendations.

**References**


ANNEX 1

List of Participants

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