[F1 ANNEX I

CHEMICAL, PHARMACEUTICAL AND ANALYTICAL STANDARDS, SAFETY AND RESIDUE TESTS, PRE-CLINICAL AND CLINICAL TRIALS IN RESPECT OF TESTING OF VETERINARY MEDICINAL PRODUCTS

Textual Amendments

F1 Substituted by Commission Directive 2009/9/EC of 10 February 2009 amending Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to medicinal products for veterinary use (Text with EEA relevance).

TITLE II

REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

PART 2:

CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL/ MICROBIOLOGICAL INFORMATION (QUALITY)

All test procedures shall fulfil the necessary criteria for analysis and control of the quality of the starting materials and the finished product and shall be validated procedures. The results of the validation studies shall be provided. Any special apparatus and equipment which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the manufacturing method.

In the case of test procedures included in the *European Pharmacopoeia* or the pharmacopoeia of a Member State, this description may be replaced by a detailed reference to the pharmacopoeia in question.

Where available, chemical and biological reference material of the *European Pharmacopoeia* shall be used. If other reference preparations and standards are used, they shall be identified and described in detail.

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

1. Qualitative particulars

'Qualitative particulars' of all the constituents of the immunological veterinary medicinal product shall mean the designation or description of:

— the active substance(s),

— the constituents of the adjuvants,

— the constituent(s) of the excipients, whatever their nature or the quantity used, including preservatives, stabilisers, emulsifiers, colouring matter, flavouring, aromatic substances, markers, etc.,

— the constituents of the pharmaceutical form administered to animals.

These particulars shall be supplemented by any relevant data concerning the container and, where appropriate, its manner of closure, together with details of devices with which the immunological veterinary medicinal product will be used or administered and which will be delivered with the medicinal product. If the device is not delivered together with the immunological veterinary medicinal product, relevant information about the device shall be provided, where necessary for the assessment of the product.

2. 'Usual terminology'

The 'usual terminology', to be used in describing the constituents of immunological veterinary medicinal products, shall mean, notwithstanding the application of the other provisions of Article 12(3)(c):

— in respect of substances which appear in the *European Pharmacopoeia* or, failing this, in the pharmacopoeia of one of the Member States, the main title of the monograph in question, which will be obligatory for all such substances, with reference to the pharmacopoeia concerned,

— in respect of other substances, the international non-proprietary name recommended by the World Health Organisation, which may be accompanied by another non-proprietary name or, failing these, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,

— in respect of colouring matter, designation by the 'E' code assigned to them in Directive 78/25/EEC.

3. Quantitative particulars

In order to give the 'quantitative particulars' of the active substances of an immunological veterinary medicinal product, it is necessary to specify whenever possible the number of organisms, the specific protein content, the mass, the number of International Units (IU) or units of biological activity, either per dosage-unit or volume, and with regard to the adjuvant and to the constituents of the excipients, the mass or the volume of each of them, with due allowance for the details provided in Section B.

Where an international unit of biological activity has been defined, this shall be used.

The units of biological activity for which no published data exist shall be expressed in such a way as to provide unambiguous information on the activity of the ingredients, e.g. by stating the immunological effect on which the method of determining the dose is based.

4. Product development

An explanation shall be provided with regard to the composition, components and containers, supported by scientific data on product development. The overage, with justification thereof, shall be stated.

B. DESCRIPTION OF MANUFACTURING METHOD

The description of the manufacturing method accompanying the application for marketing authorisation pursuant to Article 12(3)(d), shall be drafted in such a way as to give an adequate description of the nature of the operations employed.

For this purpose the description shall include at least:

— the various stages of manufacture (including production of the antigen and purification procedures) so that an assessment can be made of the reproducibility of the manufacturing procedure and of the risks of adverse effects on the finished products,

such as microbiological contamination; the validation of key stages in the production process shall be demonstrated and the validation of the production process as a whole shall be demonstrated with provision of results of three consecutive batches produced using the method described,

— in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity and consistency of each batch of the finished product,

— listing of all the substances at the appropriate steps where they are used, including those which cannot be recovered in the course of manufacturing,

— the details of the blending, with the quantitative particulars of all the substances used,

— a statement of the stages of manufacture at which sampling is carried out for control tests during production.

C. PRODUCTION AND CONTROL OF STARTING MATERIALS

For the purposes of this paragraph ‘starting materials’ means all components used in the production of the immunological veterinary medicinal product. Culture media consisting of several components used for production of the active substance shall be regarded as one starting material. Nevertheless, the qualitative and quantitative composition of the any culture media shall be presented in so far as the authorities consider that this information is relevant to the quality of the finished product and any risks that might be posed. If materials of animal origin are used for preparation of these culture media, the animal species and the tissue used have to be included.

The dossier shall include the specifications, information on the tests to be conducted for the quality control of all batches of starting materials and results for a batch for all components used and shall be submitted in accordance with the following provisions.

1. Starting materials listed in pharmacopoeias

The monographs of the *European Pharmacopoeia* shall be applicable to all starting materials appearing in it.

In respect of other substances, each Member State may require observance of its own national pharmacopoeia with regard to products manufactured in its territory.

Constituents fulfilling the requirements of the *European Pharmacopoeia* or the pharmacopoeia of one of the Member States shall be deemed to comply sufficiently with Article 12(3)(i). In this case the description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

Colouring matter shall, in all cases, satisfy the requirements of Directive 78/25/EEC.

The routine tests carried out on each batch of starting materials must be as stated in the application for marketing authorisation. If tests other than those mentioned in the pharmacopoeia are used, proof must be supplied that the starting materials meet the quality requirements of that pharmacopoeia.

In cases where a specification or other provisions contained in a monograph of the *European Pharmacopoeia* or in the pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the applicant for marketing authorisation. The alleged insufficiency shall be reported to the authorities responsible for the pharmacopoeia in question.

In cases where a starting material is described neither in the *European Pharmacopoeia* nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted; in such cases, the applicant shall submit a copy of the

monograph accompanied where necessary by the validation of the test procedures contained in the monograph and by a translation where appropriate.

When starting materials of animal origin are used, they shall comply with the relevant monographs including general monographs and general chapters of the *European Pharmacopoeia*. The tests and controls conducted shall be appropriate to the starting material.

The applicant shall supply documentation to demonstrate that the starting materials and the manufacturing of the veterinary medical product is in comply with the requirements of the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, as well as with the requirements of the corresponding monograph of the *European Pharmacopoeia*. Certificates of Suitability issued by the European Directorate for the Quality of Medicines and HealthCare, with reference to the relevant monograph of the *European Pharmacopoeia*, may be used to demonstrate compliance.

2. Starting materials not listed in a pharmacopoeia

2.1. Starting materials of biological origin

The description shall be given in the form of a monograph.

Whenever possible, vaccine production shall be based on a seed lot system and on established cell seeds. For the production of immunological veterinary medicinal products consisting of serums, the origin, general health and immunological status of the producing animals shall be indicated and defined pools of source materials shall be used.

The origin, including geographical region, and history of starting materials shall be described and documented. For genetically engineered starting materials this information shall include details such as the description of the starting cells or strains, the construction of the expression vector (name, origin, function of the replicon, promoter enhancer and other regulator elements), control of the sequence of DNA or RNA effectively inserted, oligonucleotidic sequences of plasmid vector in cells, plasmid used for cotransfection, added or deleted genes, biological properties of the final construct and the genes expressed, copy number and genetic stability.

Seed materials, including cell seeds and raw serum for anti-serum production shall be tested for identity and extraneous agents.

Information shall be provided on all substances of biological origin used at any stage in the manufacturing procedure. The information shall include:

— details of the source of the materials,

— details of any processing, purification and inactivation applied, with data on the validation of these process and controls during production,

— details of any tests for contamination carried out on each batch of the substance.

If the presence of extraneous agents is detected or suspected, the corresponding material shall be discarded or used in very exceptional circumstances only when further processing of the product ensures their elimination and/or inactivation; elimination and/or inactivation of such extraneous agents shall be demonstrated.

When cell seeds are used, the cell characteristics shall be shown to have remained unchanged up to the highest passage level used for the production.

For live attenuated vaccines, proof of the stability of the attenuation characteristics of the seed has to be given.

Documentation shall be supplied to demonstrate that the seed materials, cell seeds, batches of serum and other material originating from animal species relevant for the transmission of TSE

comply with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, as well as with the corresponding monograph of the *European Pharmacopoeia*. Certificates of Suitability issued by the European Directorate for the Quality of Medicines and HealthCare, with reference to the relevant monograph of the *European Pharmacopoeia*, can be used to demonstrate compliance.

When required, samples of the biological starting material or reagents used in the testing procedures shall be provided to enable the competent authority to arrange for check tests to be carried out.

2.2. Starting materials of non-biological origin

The description shall be given in the form of a monograph under the following headings:

— the name of the starting material meeting the requirements of point 2 of Section A shall be supplemented by any trade or scientific synonyms,

— the description of the starting material, set down in a form similar to that used in a descriptive item in the *European Pharmacopoeia*,

— the function of the starting material,

— methods of identification,

— any special precautions which may be necessary during storage of the starting material and, if necessary, its storage life shall be given.

D. CONTROL TESTS DURING THE MANUFACTURING PROCESS

1. The dossier shall include particulars relating to the control tests, which are carried out on intermediate products with a view to verifying the consistency of the manufacturing process and the final product.

2. For inactivated or detoxified vaccines, inactivation or detoxification shall be tested during each production run as soon as possible after the end of the inactivation or detoxification process and after neutralisation if this occurs, but before the next step of production.

E. CONTROL TESTS ON THE FINISHED PRODUCT

For all tests, the description of the techniques for analysing the finished product shall be set out in sufficiently precise detail for quality assessment.

The dossier shall include particulars relating to control tests on the finished product. Where appropriate monographs exist, if test procedures and limits other than those mentioned in the monographs of the *European Pharmacopoeia*, or failing this, in the pharmacopoeia of a Member State, are used, proof must be supplied that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned. The application for marketing authorisation shall list those tests, which are carried out on representative samples of each batch of finished product. The frequency of the tests, which are not carried out on each batch, shall be stated. Release limits shall be indicated.

Where available, chemical and biological reference material of the *European Pharmacopoeia* shall be used. If other reference preparations and standards are used, they shall be identified and described in detail.

1. General characteristics of the finished product

The tests of general characteristics shall, wherever applicable, relate to the control of average masses and maximum deviations, to mechanical, physical or chemical tests,

physical characteristics such as density, pH, viscosity, etc. For each of these characteristics, specifications, with appropriate confidence limits, shall be established by the applicant in each particular case.

2. Identification of active substance(s)

Where necessary, a specific test for identification shall be carried out.

3. Batch titre or potency

A quantification of the active substance shall be carried out on each batch to show that each batch will contain the appropriate potency or titre to ensure its safety and efficacy.

4. Identification and assay of adjuvants

Insofar as testing procedures are available, the quantity and nature of the adjuvant and its components shall be verified on the finished product.

5. Identification and assay of excipient components

Insofar as is necessary, the excipient(s) shall be subject at least to identification tests.

An upper and lower limit test shall be obligatory in respect of preserving agents. An upper limit test for any other excipient components liable to give rise to an adverse reaction shall be obligatory.

6. Safety tests

Apart from the results of tests submitted in accordance with Part 3 of this Title (Safety Tests), particulars of the batch safety tests shall be submitted. These tests shall preferably be overdosage studies carried out in at least one of the most sensitive target species and by at least the recommended route of administration posing the greatest risk. Routine application of the batch safety test may be waived in the interests of animal welfare when a sufficient number of consecutive production batches have been produced and been found to comply with the test.

7. Sterility and purity test

Appropriate tests to demonstrate the absence of contamination by extraneous agents or other substances shall be carried out according to the nature of the immunological veterinary medicinal product, the method and the conditions of manufacture. If fewer tests than required by the relevant *European Pharmacopoeia* are routinely employed for each batch, the tests carried out shall be critical to the compliance with the monograph. Proof must be supplied that the immunological veterinary medicinal product would meet the requirements, if fully tested according to the monograph.

8. Residual humidity

Each batch of lyophilised product shall be tested for residual humidity.

9. Inactivation

For inactivated vaccines, a test to verify inactivation shall be carried out on the product in the final container unless it has been conducted at a late stage in-process.

F. BATCH-TO-BATCH CONSISTENCY

In order to ensure that quality of the product is consistent from batch to batch and to demonstrate conformity with specifications a full protocol of three consecutive batches giving the results for all tests performed during production and on the finished product shall be provided.

G. STABILITY TESTS

The particulars and documents accompanying the application for marketing authorisation pursuant to Article 12(3)(f) and (i) shall be submitted in accordance with the following requirements.

A description shall be given of the tests undertaken to support the shelf life proposed by the applicant. These tests shall always be real-time studies; they shall be carried out on a sufficient number of batches produced according to the described production process and on products stored in the final container(s); these tests include biological and physico-chemical stability tests.

The conclusions shall contain the results of analyses, justifying the proposed shelf life under all proposed storage conditions.

In the case of products administered in feed, information shall also be given as necessary on the shelf life of the product, at the different stages of mixing, when mixed in accordance with the recommended instructions.

Where a finished product requires reconstitution prior to administration or is administered in drinking water, details of the proposed shelf life are required for the product reconstituted as recommended. Data in support of the proposed shelf life for the reconstituted product shall be submitted.

Stability data obtained from combined products may be used as preliminary data for derivative products containing one or more of the same components.

The proposed in-use shelf life shall be justified.

The efficacy of any preservative system shall be demonstrated.

Information on the efficacy of preservatives in other similar immunological veterinary medicinal products from the same manufacturer may be sufficient.

H. OTHER INFORMATION

Information relating to the quality of the immunological veterinary medicinal product not covered by the previous sections may be included in the dossier.**]**