ISSN 1725-2555

Official Journal of the European Union

L 44

English edition

Legislation

Volume 52

14 February 2009

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[1] Text with EEA relevance

I

(Acts adopted under the EC Treaty/Euratom Treaty whose publication is obligatory)

REGULATIONS

COMMISSION REGULATION (EC) No 128/2009

of 13 February 2009

establishing the standard import values for determining the entry price of certain fruit and vegetables

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Regulation (EC) No 1234/2007 of 22 October 2007 establishing a common organisation of agricultural markets and on specific provisions for certain agricultural products (Single CMO Regulation) [1],

Having regard to Commission Regulation (EC) No 1580/2007 of 21 December 2007 laying down implementing rules for Council Regulations (EC) No 2200/96, (EC) No 2201/96 and (EC) No 1182/2007 in the fruit and vegetable sector [2], and in particular Article 138(1) thereof,

Whereas:

Regulation (EC) No 1580/2007 lays down, pursuant to the outcome of the Uruguay Round multilateral trade negotiations, the criteria whereby the Commission fixes the standard values for imports from third countries, in respect of the products and periods stipulated in Annex XV, Part A thereto,

HAS ADOPTED THIS REGULATION:

Article 1

The standard import values referred to in Article 138 of Regulation (EC) No 1580/2007 are fixed in the Annex hereto.

Article 2

This Regulation shall enter into force on 14 February 2009.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 13 February 2009.

For the Commission

Jean-Luc DEMARTY

Director-General for Agriculture and Rural Development

[1] OJ L 299, 16.11.2007, p. 1.
[2] OJ L 350, 31.12.2007, p. 1.

ANNEX

Standard import values for determining the entry price of certain fruit and vegetables

(EUR/100 kg)

CN code	Third country code (1)	Standard import value
0702 00 00	IL	111,0
	JO	68,6
	MA	42,1
	TN	134,4
	TR	97,7
	ZZ	90,8
0707 00 05	JO	170,1
	MA	134,2
	TR	159,7
	ZZ	154,7
0709 90 70	MA	83,6
	TR	152,3
	ZZ	118,0
0709 90 80	EG	164,4
	ZZ	164,4
0805 10 20	EG	49,0
	IL	50,7
	MA	61,6
	TN	44,0
	TR	55,8
	ZZ	52,2
0805 20 10	IL	145,9
	MA	89,3
	ZZ	117,6
0805 20 30, 0805 20 50, 0805 20 70, 0805 20 90	CN	72,2
	IL	91,5
	MA	158,6
	PK	47,5
	TR	64,0
	ZZ	86,8
0805 50 10	EG	44,9
	MA	55,8
	TR	53,7
	ZZ	51,5
0808 10 80	CA	90,4
	CL	67,8
	CN	79,2
	MK	32,6
	US	105,4
	ZZ	75,1
0808 20 50	AR	118,6
	CL	79,6
	CN	57,6
	US	116,6
	ZA	122,3
	ZZ	98,9

(1) Nomenclature of countries laid down by Commission Regulation (EC) No 1833/2006 (OJ L 354, 14.12.2006, p. 19). Code 'ZZ' stands for 'of other origin'.

COMMISSION REGULATION (EC) No 129/2009

of 13 February 2009

amending Regulation (EC) No 197/2006 as regards the validity of the transitional measures relating to former foodstuffs

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Regulation (EC) No 1774/2002 of the European Parliament and of the Council of 3 October 2002 laying down health rules concerning animal by-products not intended for human consumption [1], and in particular Article 32(1) thereof,

Whereas:

(1) Regulation (EC) No 1774/2002 introduces a comprehensive framework for the collection, use and disposal of animal by-products.

(2) Commission Regulation (EC) No 197/2006 of 3 February 2006 on transitional measures under Regulation (EC) No 1774/2002 as regards the collection, transport, treatment, use and disposal of former foodstuffs [2] sets out a number of transitional measures that are due to expire on 31 July 2009.

(3) The Commission has adopted a proposal for the revision of Regulation (EC) No 1774/2002 [3]. That proposal is now under consideration by the legislators and the rules relating to former foodstuffs and the available scientific evidence related to the risks arising from such animal by-products will be considered in that context. Therefore, it is appropriate to extend the period of validity of the current transitional measure so that until the adoption of new rules, the current rules relating to former foodstuffs remain applicable.

(4) In the light of the date proposed by the Commission for the entry into application of a revised Regulation on animal by-products, it is appropriate to extend the period of validity of Regulation (EC) No 197/2006 until 31 July 2011.

(5) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on the Food Chain and Animal Health,

HAS ADOPTED THIS REGULATION:

Article 1

In Article 5 of Regulation (EC) No 197/2006, the date '31 July 2009' is replaced by the date '31 July 2011'.

Article 2

This Regulation shall enter into force on the third day following that of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 13 February 2009.

For the Commission
Androulla VASSILIOU
Member of the Commission

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[1] OJ L 273, 10.10.2002, p. 1.
[2] OJ L 32, 4.2.2006, p. 13.
[3] Document COM(2008) 345 final of 10 June 2008.

COMMISSION REGULATION (EC) No 130/2009

of 13 February 2009

excluding ICES Subdivisions 27 and 28.2 from certain fishing effort limitations and recording obligations for 2009, pursuant to Council Regulation (EC) No 1098/2007 establishing a multiannual plan for the cod stocks in the Baltic Sea and the fisheries exploiting those stocks

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Regulation (EC) No 1098/2007 of 18 September 2007 establishing a multiannual plan for the cod stocks in the Baltic Sea and the fisheries exploiting those stocks, amending Regulation (EEC) No 2847/93 and repealing Regulation (EC) No 779/97 [1], and in particular Article 29 (2) thereof,

Having regard to the reports submitted by Denmark, Estonia, Finland, Germany, Latvia, Lithuania, Poland and Sweden,

Having regard to the opinion of the Scientific, Technical and Economic Committee for Fisheries (STECF),

Whereas:

(1) Provisions for setting fishing effort limitations for the cod stocks in the Baltic Sea and on the recording of related fishing effort data are set out in Regulation (EC) No 1098/2007.

(2) On the basis of Regulation (EC) No 1098/2007, Annex II to Council Regulation (EC) No 1322/2008 [2] has established fishing effort limitations for 2009 in the Baltic Sea.

(3) According to Article 29(2) of Regulation (EC) No 1098/2007 the Commission may exclude Subdivisions 27 and 28.2 from the scope of certain fishing effort limitations and recording obligations when the catches of cod were below a certain threshold in the last reporting period.

(4) Taking into account the reports submitted by Member States and the advice from the STECF, Subdivisions 27 and 28.2 should be excluded in 2009 from the scope of those fishing effort limitations and recording obligations.

(5) In order to ensure that account could be taken of the latest information made available by the Member States and to allow the scientific advice to be based on the most accurate information, the ultimate date laid down in Article 29(2) of Regulation (EC) No 1098/2007 for the final conclusion concerning the need to exclude the respective Subdivisions could not be met.

(6) Regulation (EC) No 1322/2008 applies from 1 January 2009. In order to ensure coherence with that Regulation, this Regulation should apply retroactively from that date.

(7) The measures provided for in this Regulation are in accordance with the opinion of the Committee for Fisheries and Aquaculture,

HAS ADOPTED THIS REGULATION:

Article 1

Article 8(1)(b), (3), (4) and (5) and Article 13 of Regulation (EC) No 1098/2007 shall not apply to ICES Subdivisions 27 and 28.2.

Article 2

This Regulation shall enter into force on the day following that of its publication in the *Official Journal of the European Union*.

It shall apply from 1 January 2009.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 13 February 2009.

For the Commission
Joe BORG
Member of the Commission

[1] OJ L 248, 22.9.2007, p. 1.
[2] OJ L 345, 23.12.2008, p. 1.

COMMISSION REGULATION (EC) No 131/2009

of 13 February 2009

amending Regulation (EC) No 105/2008 laying down detailed rules for the application of Council Regulation (EC) No 1255/1999 as regards intervention on the market in butter

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Regulation (EC) No 1234/2007 of 22 October 2007 establishing a common organisation of agricultural markets and on specific provisions for certain agricultural products (Single CMO Regulation) [1], and in particular Article 43 in conjunction with Article 4 thereof,

Whereas:

(1) Article 10(1)(e) of Regulation (EC) No 1234/2007 provides for public intervention of butter.

(2) Commission Regulation (EC) No 105/2008 [2] has laid down the detailed rules concerning the public intervention of butter.

(3) Article 13(1)(c) in conjunction with Article 18(2)(d) of Regulation (EC) No 1234/2007 limit public intervention of butter at fixed price to a quantity offered of 30 000 tonnes for the period 1 March to 31 August.

(4) In order to comply with the limit of 30 000 tonnes it is appropriate to provide for a reflection period during which, before a decision is taken on the offers, special measures can be taken applying in particular to pending offers. Those measures may consist of closure of intervention, application of an allocation percentage and rejection of pending offers. They require swift action and the Commission should be enabled to take all necessary measures without delay.

(5) Regulation (EC) No 105/2008 should be amended accordingly.

(6) The measures provided for in this Regulation are in accordance with the opinion of the Management Committee for the Common Organisation of Agricultural Markets,

HAS ADOPTED THIS REGULATION:

Article 1

Regulation (EC) No 105/2008 is amended as follows:

1. Article 6 is replaced by the following:

'*Article 6*

Buying-in of butter at 90 % of the reference price pursuant to Article 18(1)(b) of Regulation (EC) No 1234/2007 shall be carried out in accordance with the provisions of this Section.'

2. In Article 7(5) the following subparagraph is added:

'Offers submitted on a Saturday, Sunday or public holiday shall be deemed to be received by the competent body on the first working day following the day on which they were submitted.'

3. Article 9 is amended as follows:

(a) Paragraph 1 is replaced by the following:

'1. After checking the offer, and on the fifth working day following the day of receipt of the offer to sell, the competent body shall issue a delivery order, provided that the Commission does not adopt special measures in accordance with Article 12(2).

The delivery order shall be dated and numbered and shall show:

(a) the quantity to be delivered;

(b) the final date for delivery of the butter;

(c) the cold store to which it must be delivered.

Delivery orders shall not be issued for quantities that had not been notified in accordance with Article 12(1).'

[1] OJ L 299, 16.11.2007, p. 1.
[2] OJ L 32, 6.2.2008, p. 3.

(b) Paragraph 5 is replaced by the following:

'5. For the purpose of this Article, the butter shall be deemed to be delivered to the competent body on the day when the full quantity of butter covered by the delivery order enters the cold store designated by the competent body, but no earlier than the day following that on which the delivery order was issued.'

4. Article 12 is replaced by the following:

'*Article 12*

1. Not later than 14.00 (Brussels time) each working day, the competent body shall inform the Commission of the quantities of butter which, during the preceding working day, have been the subject of an offer to sell in accordance with Article 7.

2. In order to comply with the limits referred to in Article 13(1)(c) of Regulation (EC) No 1234/2007 the Commission shall decide, without assistance of the Committee referred to in Article 195(1) of the same Regulation:

(a) to close intervention buying-in at fixed price;

(b) where acceptance of the full quantity offered on a certain day would lead to the maximum quantity being exceeded, to set a single percentage by which the quantities in the offers received on that day are reduced;

(c) where appropriate, to reject offers for which no delivery order has been issued.

By way of derogation from Article 7(6), a seller which is subject to a reduced acceptance of his offer as referred to in point (b) of this paragraph may decide to withdraw his offer within five working days from the publication of the regulation fixing the reduction percentage.'

5. In Article 13, paragraph 1 is replaced by the following:

'1. Where the Commission decides in accordance with the procedure referred to in Article 195(2) of Regulation (EC) No 1234/2007 to start buying-in butter by means of a tendering procedure pursuant to Articles 13(3) and 18(2)(d) of that Regulation, Article 2 and Article 3(1)(2)(4)(5) and (6) and Articles 4, 5, 9, 10 and 11 of this Regulation shall apply unless otherwise provided in this Section.'

6. In Article 16(2), the first subparagraph is replaced by the following:

'In the light of the tenders received for each invitation to tender, the Commission shall fix a maximum buying-in price, in accordance with the procedure referred to in Article 195(2) of Regulation (EC) No 1234/2007.'

7. In Article 18 the following paragraph is added:

'2a. Delivery orders shall not be issued for quantities that had not been notified in accordance with Article 16(1).'

8. In Article 20, paragraph 1 is replaced by the following:

'1. The competent body shall choose the nearest available cold store to the place where the butter is stored.

However, the competent body may choose another store situated within a distance of 350 km, provided that the choice of that cold store does not result in additional storage costs.

The competent body may choose a cold store situated beyond that distance if the resulting expenditure, including storage and transport costs, is lower. In that case the competent body shall notify the Commission of its choice forthwith.'

Article 2

This Regulation shall enter into force on the third day following that of its publication in the *Official Journal of European Union*.

It shall apply from 1 March 2009.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 13 February 2009.

For the Commission
Mariann FISCHER BOEL
Member of the Commission

COMMISSION REGULATION (EC) No 132/2009

of 13 February 2009

fixing the import duties in the cereals sector applicable from 16 February 2009

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Regulation (EC) No 1234/2007 of 22 October 2007 establishing a common organisation of agricultural markets and on specific provisions for certain agricultural products (Single CMO Regulation) ([1]),

Having regard to Commission Regulation (EC) No 1249/96 of 28 June 1996 laying down detailed rules for the application of Council Regulation (EEC) No 1766/92 in respect of import duties in the cereals sector ([2]), and in particular Article 2(1) thereof,

Whereas:

(1) Article 136(1) of Regulation (EC) No 1234/2007 states that the import duty on products falling within CN codes 1001 10 00, 1001 90 91, ex 1001 90 99 (high quality common wheat), 1002, ex 1005 other than hybrid seed, and ex 1007 other than hybrids for sowing, is to be equal to the intervention price valid for such products on importation increased by 55 %, minus the cif import price applicable to the consignment in question. However, that duty may not exceed the rate of duty in the Common Customs Tariff.

(2) Article 136(2) of Regulation (EC) No 1234/2007 lays down that, for the purposes of calculating the import duty referred to in paragraph 1 of that Article, representative cif import prices are to be established on a regular basis for the products in question.

(3) Under Article 2(2) of Regulation (EC) No 1249/96, the price to be used for the calculation of the import duty on products of CN codes 1001 10 00, 1001 90 91, ex 1001 90 99 (high quality common wheat), 1002 00, 1005 10 90, 1005 90 00 and 1007 00 90 is the daily cif representative import price determined as specified in Article 4 of that Regulation.

(4) Import duties should be fixed for the period from 16 February 2009 and should apply until new import duties are fixed and enter into force,

HAS ADOPTED THIS REGULATION:

Article 1

From 16 February 2009, the import duties in the cereals sector referred to in Article 136(1) of Regulation (EC) No 1234/2007 shall be those fixed in Annex I to this Regulation on the basis of the information contained in Annex II.

Article 2

This Regulation shall enter into force on 16 February 2009.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 13 February 2009.

For the Commission

Jean-Luc DEMARTY

Director-General for Agriculture and Rural Development

([1]) OJ L 299, 16.11.2007, p. 1.
([2]) OJ L 161, 29.6.1996, p. 125.

ANNEX I

Import duties on the products referred to in Article 136(1) of Regulation (EC) No 1234/2007 applicable from 16 February 2009

CN code	Description	Import duties [1] (EUR/t)
1001 10 00	Durum wheat, high quality	0,00
	medium quality	0,00
	low quality	0,00
1001 90 91	Common wheat seed	0,00
ex 1001 90 99	High quality common wheat, other than for sowing	0,00
1002 00 00	Rye	22,25
1005 10 90	Maize seed other than hybrid	16,32
1005 90 00	Maize, other than seed [2]	16,32
1007 00 90	Grain sorghum other than hybrids for sowing	22,25

[1] For goods arriving in the Community via the Atlantic Ocean or via the Suez Canal the importer may benefit, under Article 2(4) of Regulation (EC) No 1249/96, from a reduction in the duty of:

— 3 EUR/t, where the port of unloading is on the Mediterranean Sea, or

— 2 EUR/t, where the port of unloading is in Denmark, Estonia, Ireland, Latvia, Lithuania, Poland, Finland, Sweden, the United Kingdom or the Atlantic coast of the Iberian peninsula.

[2] The importer may benefit from a flatrate reduction of EUR 24 per tonne where the conditions laid down in Article 2(5) of Regulation (EC) No 1249/96 are met.

ANNEX II

Factors for calculating the duties laid down in Annex I

30.1.2009-12.2.2009

1. Averages over the reference period referred to in Article 2(2) of Regulation (EC) No 1249/96:

(EUR/t)

	Common wheat (1)	Maize	Durum wheat, high quality	Durum wheat, medium quality (2)	Durum wheat, low quality (3)	Barley
Exchange	Minnéapolis	Chicago	—	—	—	—
Quotation	199,16	113,47	—	—	—	—
Fob price USA	—	—	235,88	225,88	205,88	125,81
Gulf of Mexico premium	57,14	18,28	—	—	—	—
Great Lakes premium	—	—	—	—	—	—

(1) Premium of 14 EUR/t incorporated (Article 4(3) of Regulation (EC) No 1249/96).
(2) Discount of 10 EUR/t (Article 4(3) of Regulation (EC) No 1249/96).
(3) Discount of 30 EUR/t (Article 4(3) of Regulation (EC) No 1249/96).

2. Averages over the reference period referred to in Article 2(2) of Regulation (EC) No 1249/96:

Freight costs: Gulf of Mexico–Rotterdam:	11,82 EUR/t
Freight costs: Great Lakes–Rotterdam:	10,45 EUR/t

DIRECTIVES

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)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products [1], and in particular Article 88 thereof,

Whereas:

(1) In order to be placed on the European Community market, a veterinary medicinal product must be granted a marketing authorisation by a competent authority. For this purpose, an application dossier containing particulars and documents relating to the results of tests and trials carried out on the veterinary medicinal product must be submitted.

(2) The purpose of Annex I to Directive 2001/82/EC is to lay down detailed scientific and technical requirements regarding the testing of veterinary medicinal products against which the quality, safety and efficacy of the veterinary medicinal product should be assessed. It also gives instructions concerning the presentation and content of the application dossier.

(3) The detailed scientific and technical requirements of Annex I to Directive 2001/82/EC need to be adapted to take account of scientific and technical progress and in particular of a set of new requirements resulting from recent legislation. The presentation and content of the marketing authorisation application dossier should be improved in order to facilitate the assessment and the better use of certain parts of the dossier which are common to several veterinary medicinal products.

(4) In order to simplify current procedures for the assessment of veterinary vaccines, both for the granting of a first marketing authorisation and for the subsequent changes to it due to modifications to the manufacturing process and testing of individual antigens involved in combined vaccines, a new system based on the concept of a master file (Vaccine Antigen Master File, VAMF) should be introduced for vaccines which involve several antigens.

(5) To permit authorisation of vaccines against antigenically variable viruses in a way that ensures that the most effective measures can be taken swiftly by the Community against the incursion or spread of epizootic diseases, the concept of multi-strain dossier should be introduced. This will at the same time ensure that marketing authorisations are granted on the basis of objective scientific criteria of quality, safety and efficacy.

(6) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee for Veterinary Medicinal Products,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Annex I to Directive 2001/82/EC is replaced by the text set out in the Annex to this Directive.

Article 2

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 6 September 2009 at the latest. They shall forthwith communicate to the Commission the text of those provisions and a correlation table between those provisions and this Directive.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

[1] OJ L 311, 28.11.2001, p. 1.

Article 3

This Directive shall enter into force on the 20th day following its publication in the *Official Journal of the European Union*.

Article 4

This Directive is addressed to the Member States.

Done at Brussels, 10 February 2009.

For the Commission
Günter VERHEUGEN
Vice-President

ANNEX

'ANNEX I

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

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INTRODUCTION AND GENERAL PRINCIPLES

1. The particulars and documents accompanying an application for marketing authorisation pursuant to Articles 12 to 13d shall be presented in accordance with the requirements set out in this Annex and shall take into account the guidance published by the Commission in *The rules governing medicinal products in the European Union*, Volume 6 B, Notice to applicants, Veterinary medicinal products, Presentation and Contents of the Dossier.

2. In assembling the dossier for application for marketing authorisation, applicants shall also take into account the current state of veterinary medicinal knowledge and the scientific guidelines relating to the quality, safety and efficacy of veterinary medicinal products published by the European Medicines Agency (Agency) and the other pharmaceutical Community guidelines published by the Commission in different volumes of *The rules governing medicinal products in the European Union*.

3. For veterinary medicinal products other than immunological veterinary medicinal products, with respect to the quality (pharmaceutical) part (physico-chemical, biological and microbiological tests) of the dossier, all relevant monographs including general monographs and the general chapters of the *European Pharmacopoeia* are applicable. For immunological veterinary medicinal products, with respect to the quality, safety and efficacy parts of the dossier, all relevant monographs including general monographs and the general chapters of the *European Pharmacopoeia* are applicable.

4. The manufacturing process shall comply with the requirements of Commission Directive 91/412/EEC [1] laying down the principles and guidelines for veterinary medicinal products and with the principles and guidelines on Good Manufacturing Practice (GMP), published by the Commission in *The rules governing medicinal products in the European Union*, Volume 4.

5. All information which is relevant to the evaluation of the veterinary medicinal product concerned shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned test or trial relating to the veterinary medicinal product.

6. Pharmacological, toxicological, residue and safety tests shall be carried out in conformity with the provisions related to Good Laboratory Practice (GLP) laid down in Directive 2004/10/EC of the European Parliament and of the Council [2] and Directive 2004/9/EC of the European Parliament and of the Council [3].

7. Member States shall ensure that all experiments on animals are conducted in accordance with Council Directive 86/609/EEC [4].

8. In order to monitor the risk/benefit assessment, any new information not in the original application and all pharmacovigilance information shall be submitted to the competent authority. After marketing authorisation has been granted, any change to the content of the dossier shall be submitted to the competent authorities in accordance with Commission Regulations (EC) No 1084/2003 [5] or (EC) No 1085/2003 [6] for veterinary medicinal products authorised as defined in Article 1 of those Regulations, respectively.

9. The environmental risk assessment connected with the release of veterinary medicinal products containing or consisting of Genetically Modified Organisms (GMOs) within the meaning of Article 2 of Directive 2001/18/EC of the European Parliament and of the Council [7] shall be provided in the dossier. The information shall be presented in accordance with the provisions of Directive 2001/18/EC and Regulation (EC) No 726/2004 of the European Parliament and of the Council [8], taking into account guidance documents published by the Commission.

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[1] OJ L 228, 17.8.1991, p. 70.
[2] OJ L 50, 20.2.2004, p. 44.
[3] OJ L 50, 20.2.2004, p. 28.
[4] OJ L 358, 18.12.1986, p. 1.
[5] OJ L 159, 27.6.2003, p. 1.
[6] OJ L 159, 27.6.2003, p. 24.
[7] OJ L 106, 17.4.2001, p. 1.
[8] OJ L 136, 30.4.2004, p. 1.

10. In cases of applications for marketing authorisations for veterinary medicinal products indicated for animal species and indications representing smaller market sectors, a more flexible approach may be applicable. In such cases, relevant scientific guidelines and/or scientific advice should be taken into account.

This Annex is divided in four titles:

Title I describes the standardised requirements for applications for veterinary medicinal products other than immunological veterinary medicinal products.

Title II describes the standardised requirements for applications for immunological veterinary medicinal products.

Title III describes specific types of marketing authorisation dossiers and requirements.

Title IV describes the dossier requirements for particular types of veterinary medicinal products.

TITLE I

REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

The following requirements shall apply to veterinary medicinal products other than immunological veterinary medicinal products, except where otherwise set out in Title III.

PART 1: *SUMMARY OF THE DOSSIER*

A. ADMINISTRATIVE INFORMATION

The veterinary medicinal product, which is the subject of the application, shall be identified by its name and by the name of the active substance(s), together with the strength, the pharmaceutical form, the route and method of administration (see Article 12(3)(f) of Directive) and a description of the final presentation of the product, including packaging, labelling and package leaflet (see Article 12(3)(l) of Directive).

The name and address of the applicant shall be given, together with the name and address of the manufacturers and the sites involved in the different stages of the manufacture, testing and release (including the manufacturer of the finished product and the manufacturer(s) of the active substance(s)), and where relevant the name and address of the importer.

The applicant shall identify the number and titles of volumes of documentation submitted in support of the application and indicate what samples, if any, are also provided.

Annexed to the administrative information shall be a document showing that the manufacturer is authorised to produce the veterinary medicinal products concerned, as defined in Article 44, together with a list of countries in which authorisation has been granted, copies of all the summaries of product characteristics in accordance with Article 14 as approved by Member States and a list of countries in which an application has been submitted or refused.

B. SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The applicant shall propose a summary of the product characteristics, in accordance with Article 14 of this Directive.

A proposed labelling text for the immediate and outer packaging shall be provided in accordance with Title V of this Directive, together with a package leaflet where one is required pursuant to Article 61. In addition the applicant shall provide one or more specimens or mock-ups of the final presentation(s) of the veterinary medicinal product in at least one of the official languages of the European Union; the mock-up may be provided in black and white and electronically where prior agreement from the competent authority has been obtained.

C. DETAILED AND CRITICAL SUMMARIES

In accordance with Article 12(3), detailed and critical summaries shall be provided on the results of pharmaceutical (physico-chemical, biological or microbiological) tests, of the safety tests and residue tests, of the pre-clinical and clinical trials and of the tests assessing the potential risks posed by the veterinary medicinal product for the environment.

Each detailed and critical summary shall be prepared in the light of the state of scientific knowledge at the time of submission of the application. It shall contain an evaluation of the various tests and trials, which constitute the marketing authorisation dossier, and shall address all points relevant to the assessment of the quality, safety and efficacy of the veterinary medicinal product. It shall give detailed results of the tests and trials submitted and precise bibliographic references.

All important data shall be summarised in an appendix, whenever possible in tabular or graphic form. The detailed and critical summaries and the appendices shall contain precise cross references to the information contained in the main documentation.

The detailed and critical summaries shall be signed and dated, and information about the author's educational background, training and occupational experience shall be attached. The professional relationship of the author with the applicant shall be declared.

Where the active substance has been included in a medicinal product for human use authorised in accordance with the requirements of Annex I to Directive 2001/83/EC of the European Parliament and of the Council [1] the overall quality summary provided for in Module 2, section 2.3 of that Annex may replace the summary regarding the documentation related to the active substance or the product, as appropriate.

Where the competent authority has publicly announced that the chemical, pharmaceutical and biological/microbiological information for the finished product may be included in the dossier in the Common Technical Document (CTD) format only, the detailed and critical summary on the results of pharmaceutical tests may be presented in the quality overall summary format.

In the case of application for an animal species or for indications representing smaller market sectors, the quality overall summary format may be used without prior agreement of the competent authorities.

PART 2: *PHARMACEUTICAL (PHYSICO-CHEMICAL, BIOLOGICAL OR MICROBIOLOGICAL INFORMATION (QUALITY))*

Basic principles and requirements

The particulars and documents which shall accompany the application for marketing authorisation pursuant to the first indent of Article 12(3)(j) shall be submitted in accordance with the requirements below.

The pharmaceutical (physico-chemical, biological or microbiological) data shall include for the active substance(s) and for the finished veterinary medicinal product information on the manufacturing process, the characterisation and properties, the quality control procedures and requirements, the stability as well as a description of the composition, the development and presentation of the veterinary medicinal product.

All monographs, including general monographs and general chapters of the *European Pharmacopoeia*, or failing that, of a Member State are applicable.

All test procedures shall fulfil the criteria for analysis and control of the quality of the starting materials and the finished product and should take account of established guidance and requirements. The results of the validation studies shall be provided.

All the test procedure(s) shall be described in sufficiently precise detail so as to be reproducible in control tests, carried out at the request of the competent authority; 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 method of preparation. 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 relevant, 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] OJ L 311, 28.11.2001, p. 67.

In cases where the active substance has been included in a medicinal product for human use authorised in accordance with the requirements of Annex I to Directive 2001/83/EC the chemical, pharmaceutical and biological/microbiological information provided for in Module 3 of that Directive may replace the documentation related to the active substance or the finished product, as appropriate.

The chemical, pharmaceutical and biological/microbiological information for the active substance or the finished product may be included in the dossier in CTD format only where the competent authority has publicly announced this possibility.

In the case of any application for an animal species or for indications representing smaller market sectors the CTD format may be followed without prior agreement of the competent authorities.

A. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

1. **Qualitative particulars**

"Qualitative particulars" of all the constituents of the medicinal product shall mean the designation or description of:

— the active substance(s),

— the constituents of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances,

— the constituents, intended to be ingested or otherwise administered to animals, of the outer covering of the veterinary medicinal products, such as capsules, gelatine capsules.

These particulars shall be supplemented by any relevant data concerning the immediate packaging and if relevant the secondary packaging and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be supplied with the medicinal product.

2. **Usual terminology**

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

— in respect of constituents which appear in the *European Pharmacopoeia* or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,

— in respect of other constituents, the international non-proprietary name (INN) recommended by the World Health Organisation (WHO), which may be accompanied by another non-proprietary name, or, failing these, the exact scientific designation; constituents 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 by Council Directive 78/25/EEC [1].

3. **Quantitative particulars**

3.1. In order to give "quantitative particulars" of all the active substances of the veterinary medicinal products, it is necessary, depending on the pharmaceutical form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance.

[1] OJ L 11, 14.1.1978, p. 18.

Units of biological activity shall be used for substances, which cannot be defined chemically. Where an International Unit of biological activity has been defined by the World Health Organisation, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using where applicable the *European Pharmacopoeia* Units.

Whenever possible, biological activity per units of mass or volume shall be indicated. This information shall be supplemented:

— in respect of single-dose preparations, by the mass or units of biological activity of each active substance in the unit container, taking into account the usable volume of the product, after reconstitution, where appropriate,

— in respect of veterinary medicinal products to be administered by drops, by the mass or units of biological activity of each active substance contained per drop or contained in the number of drops corresponding to 1 ml or 1 g of the preparation,

— in respect of syrups, emulsions, granular preparations and other pharmaceutical forms to be administered in measured quantities, by the mass or units of biological activity of each active substance per measured quantity.

3.2. Active substances present in the form of compounds or derivatives shall be described quantitatively by their total mass, and if necessary or relevant, by the mass of the active entity or entities of the molecule.

3.3. For veterinary medicinal products containing an active substance which is the subject of an application for marketing authorisation in any Member State for the first time, the quantitative statement of an active substance which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorised veterinary medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active substance.

4. **Development pharmaceutics**

An explanation shall be provided with regard to the choice of composition, constituents, immediate packaging, possible further packaging, outer packaging if relevant, the intended function of the excipients in the finished product and the method of manufacture of the finished product. This explanation shall be supported by scientific data on development pharmaceutics. The overage, with justification thereof, shall be stated. The microbiological characteristics (microbiological purity and antimicrobial activity) and usage instructions shall be proven to be appropriate for the intended use of the veterinary medicinal product as specified in the marketing authorisation application dossier.

B. DESCRIPTION OF THE MANUFACTURING METHOD

The name, address and responsibility of each manufacturer and each proposed production site or facility involved in manufacturing and testing shall be indicated.

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 synopsis of the nature of the operations employed.

For this purpose it shall include at least:

— mention of the various stages of manufacture, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents,

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

— the actual manufacturing formula, with the quantitative particulars of all the substances used, the quantities of excipients, however, being given in approximate terms insofar as the pharmaceutical form makes this necessary; mention shall be made of any substances that may disappear in the course of manufacture; any overage shall be indicated and justified,

— a statement of the stages of manufacture at which sampling is carried out for in-process control tests and the limits applied, where other data in the documents supporting the application show such tests to be necessary for the quality control of the finished product,

— experimental studies validating the manufacturing process and where appropriate a process validation scheme for production scale batches,

— for sterile products, where non-pharmacopoeial standard sterilisation conditions are used, details of the sterilisation processes and/or aseptic procedures used.

C. CONTROL OF STARTING MATERIALS

1. **General requirements**

For the purposes of this paragraph, "starting materials" shall mean all the constituents of the veterinary medicinal product and, if necessary, of its container including its closure, as referred to in Section A, point 1, above.

The dossier shall include the specifications and information on the tests to be conducted for quality control of all batches of starting materials.

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 a pharmacopoeia are used, this shall be justified by providing proof that the starting materials meet the quality requirements of that pharmacopoeia.

Where a Certificate of Suitability has been issued by the European Directorate for the Quality of Medicines and HealthCare for a starting material, active substance or excipient, this Certificate constitutes the reference to the relevant monograph of the *European Pharmacopoeia*.

Where a Certificate of Suitability is referred to, the manufacturer shall give an assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines and HealthCare.

Certificates of Analysis shall be presented for the starting materials in order to demonstrate compliance with the defined specification.

1.1. *Active substances*

The name, address, and responsibility of each manufacturer and each proposed production site or facility involved in manufacturing and testing of an active substance shall be indicated.

For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the following information to be supplied in a separate document directly to the competent authorities by the manufacturer of the active substance as an Active Substance Master File:

(a) a detailed description of the manufacturing process;

(b) a description of the quality control during manufacture;

(c) a description of the process validation.

In this case, the manufacturer shall however provide the applicant with all the data which may be necessary for the latter to take responsibility for the veterinary medicinal product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities those documents and particulars shall also be supplied to the applicant where they concern the applicant's part of the Active Substance Master File.

Additionally, information on the method of manufacture, on quality control and on impurities as well as evidence of the molecular structure shall be provided where a Certificate of Suitability for the active substance is not available:

1. Information on the manufacturing process shall include a description of the active substance manufacturing process that represents the applicant's commitment for the manufacture of the active substance. All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material is used in the process. Information on the quality and control of those materials shall be provided. Information demonstrating that materials meet standards which are appropriate for their intended use shall be provided.

2. Information on quality control shall contain tests (including acceptance criteria) carried out at every critical step, information on the quality and control of intermediates and process validation and/or evaluation studies as appropriate. It shall also contain validation data for the analytical methods applied to the active substance, where appropriate.

3. Information on impurities shall indicate predictable impurities together with the levels and nature of observed impurities. It shall also contain information on the safety of these impurities where relevant.

4. For biotechnological veterinary medicinal products, evidence of molecular structure shall include the schematic amino acid sequence and relative molecular mass.

1.1.1. Active substances listed in pharmacopoeias

The general and specific monographs of the *European Pharmacopoeia* shall be applicable to all active substances appearing in it.

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 and procedures shall be replaced in each relevant section by an appropriate reference to the pharmacopoeia in question.

In cases where a specification contained in a monograph of the *European Pharmacopoeia* or in the national pharmacopoeia of a Member State is insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the applicant, including limits for specific impurities with validated test procedures.

The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorisation holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

In the absence of a *European Pharmacopoeia* monograph for an active substance, and where the active substance is described in the pharmacopoeia of a Member State, that monograph may be applied.

In cases where an active substance is described neither in the *European Pharmacopoeia* nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia may be accepted if its suitability is demonstrated; in such cases, the applicant shall submit a copy of the monograph accompanied by a translation where appropriate. Data to demonstrate the ability of the monograph to adequately control the quality of the active substance shall be presented.

1.1.2. Active substances not in a pharmacopoeia

Constituents which are not given in any pharmacopoeia shall be described in the form of a monograph under the following headings:

(a) the name of the constituent, meeting the requirements of Section A point 2, shall be supplemented by any trade or scientific synonyms;

(b) the definition of the substance, set down in a form similar to that used in the *European Pharmacopoeia*, shall be accompanied by any necessary explanatory evidence, especially concerning the molecular structure. Where substances can only be described by their manufacturing method, the description shall be sufficiently detailed to characterise a substance which is constant both on its composition and in its effects;

(c) methods of identification may be described in the form of complete techniques as used for production of the substance, and in the form of tests which ought to be carried out as a routine matter;

(d) purity tests shall be described in relation to each individual predictable impurity, especially those which may have a harmful effect, and, if necessary, those which, having regard to the combination of substances to which the application refers, might adversely affect the stability of the medicinal product or distort analytical results;

(e) tests and limits to control parameters relevant to the finished product, such as particle size and sterility shall be described and methods shall be validated where relevant;

(f) with regard to complex substances of plant or animal origin, a distinction must be made between the case where multiple pharmacological effects render chemical, physical or biological control of the principal components necessary, and the case of substances containing one or more groups of principles having similar activity, in respect of which an overall method of assay may be accepted.

Those data shall demonstrate that the proposed set of test procedures is sufficient to control the quality of the active substance from the defined source.

1.1.3. Physico-chemical characteristics liable to affect bioavailability

The following items of information concerning active substances, whether or not listed in the pharmacopoeias, shall be provided as part of the general description of the active substances if the bioavailability of the veterinary medicinal product depends on them:

— crystalline form and solubility coefficients,

— particle size, where appropriate after pulverisation,

— state of hydration,

— oil/water coefficient of partition,

— pK/pH values.

The first three indents are not applicable to substances used solely in solution.

1.2. *Excipients*

The general and specific monographs of the *European Pharmacopoeia* shall be applicable to all substances appearing in it.

Excipients shall comply with the requirements of the appropriate *European Pharmacopoeia* monograph. Where such a monograph does not exist reference may be made to the pharmacopoeia of a Member State. In the absence of such a monograph reference may be made to the pharmacopoeia of a third country. In this case the suitability of this monograph shall be demonstrated. Where appropriate, additional tests to control parameters such as particle size, sterility, residual solvents shall supplement the requirements of the monograph. In the absence of a pharmacopoeial monograph a specification shall be proposed and justified. The requirements for specifications as set out in section 1.1.2 (a to e) for the active substance shall be followed. The proposed methods and their supporting validation data shall be presented.

Colouring matters for inclusion in veterinary medicinal products shall satisfy the requirements of Directive 78/25/EEC, except for certain veterinary medicinal products for topical use, such as insecticidal collars and ear tags, where the use of other colouring matters is justified.

Colouring matters shall meet the purity criteria as laid down in Commission Directive 95/45/EC [1].

For novel excipients, that is to say excipient(s) used for the first time in a veterinary medicinal product or by a new route of administration, details of manufacture, characterisation, and controls, with cross references to supporting safety data, both clinical and non-clinical, shall be provided.

1.3. *Container-closure systems*

1.3.1. Active substance

Information on the container-closure system for the active substance shall be given. The level of information required shall be determined by the physical state (liquid, solid) of the active substance.

1.3.2. Finished product

Information on the container-closure system for the finished product shall be given. The level of information required shall be determined by the route of administration of the veterinary medicinal product and the physical state (liquid, solid) of the dosage form.

Packaging materials shall comply with the requirements of the appropriate *European Pharmacopoeia* monograph. Where such a monograph does not exist reference may be made to the pharmacopoeia of a Member State. In the absence of such a monograph reference may be made to the Pharmacopoeia of a third country. In this case the suitability of this monograph shall be demonstrated.

In the absence of a pharmacopoeial monograph, a specification shall be proposed and justified for the packaging material.

Scientific data on the choice and suitability of the packaging material shall be presented.

For novel packaging materials in contact with the product, information on their composition, manufacture and safety shall be presented.

Specifications and, if appropriate, performance data shall be presented for any dosing or administration device supplied with the veterinary medicinal product.

1.4. *Substances of biological origin*

Where source materials such as microorganisms, tissues of either plant or animal origin, cells or fluids (including blood) of human or animal origin or biotechnological cell constructs are used in the manufacture of veterinary medicinal products, the origin and history of starting materials shall be described and documented.

The description of the starting material shall include the manufacturing strategy, purification/inactivation procedures with their validation and all in-process control procedures designed to ensure the quality, safety and batch to batch consistency of the finished product.

When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the passage level used for the production and beyond.

Seed materials, cell banks and pools of serum and, whenever possible, the source materials from which they are derived shall be tested for extraneous agents.

[1] OJ L 226, 22.9.1995, p. 1.

When starting materials of animal or human origin are used, the measures used to ensure freedom from potentially pathogenic agents shall be described.

If the presence of potentially pathogenic extraneous agents is inevitable, the material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.

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 [1], 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*, may be used to demonstrate compliance.

D. CONTROL TESTS CARRIED OUT AT INTERMEDIATE STAGES OF THE MANUFACTURING PROCESS

The dossier shall include particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the technical characteristics and the production process.

These tests are essential for checking the conformity of the veterinary medicinal product with the formula when, exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the active substances (or of all the excipient components subject to the same requirements as the active substances).

The same applies where the quality control of the finished product depends on in-process control tests, particularly if the substance is essentially defined by its manufacturing method.

Where an intermediate product may be stored prior to further processing or primary assembly, a shelf life for the intermediate product shall be defined on the basis of the data resulting from stability studies.

E. TESTS ON THE FINISHED PRODUCT

For the control of the finished product, a batch of a finished product comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.

The application for marketing authorisation shall list those tests, which are carried out routinely on each batch of finished product. The frequency of the tests which are not carried out routinely shall be stated. Release limits shall be indicated.

The dossier shall include particulars relating to control tests on the finished product at release. They shall be submitted in accordance with the following requirements.

The provisions of the relevant monographs and general chapters of the *European Pharmacopoeia*, or failing that, of a Member State, shall be applicable to all products defined therein.

If test procedures and limits other than those mentioned in the relevant monographs and general chapters of the *European Pharmacopoeia*, or failing this, in the pharmacopoeia of a Member State are used, this shall be justified by providing proof that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned.

[1] OJ C 24, 28.1.2004, p. 6.

1. **General characteristics of the finished product**

Certain tests of the general characteristics of a product shall always be included among the tests on the finished product. These tests shall, wherever applicable, relate to the control of average masses and maximum deviations, to mechanical, physical or microbiological tests, organoleptic characteristics, physical characteristics such as density, pH, refractive index. For each of these characteristics, standards and tolerance limits shall be specified by the applicant in each particular case.

The conditions of the tests, where appropriate, the equipment/apparatus employed and the standards shall be described in precise details whenever they are not given in the *European Pharmacopoeia* or the pharmacopoeia of the Member States; the same shall apply in cases where the methods prescribed by such pharmacopoeias are not applicable.

Furthermore, solid pharmaceutical forms having to be administered orally shall be subjected to *in vitro* studies on the liberation and dissolution rate of the active substance or substances, unless otherwise justified. Those studies shall also be carried out where administration is by another means if the competent authorities of the Member State concerned consider this necessary.

2. **Identification and assay of active substance(s)**

Identification and assay of the active substance(s) shall be carried out either in a representative sample from the production batch or in a number of dosage units analysed individually.

Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ± 5 % at the time of manufacture.

On the basis of the stability tests, the manufacturer shall propose and justify maximum acceptable deviation limits in the active substance content of the finished product up to the end of the proposed shelf life.

In certain cases of particularly complex mixtures, where assay of active substances which are very numerous or present in very low amounts would necessitate an intricate investigation difficult to carry out in respect of each production batch, the assay of one or more active substances in the finished product may be omitted, on the express condition that such assays are made at intermediate stages in the production process. This simplified technique may not be extended to the characterisation of the substances concerned. It shall be supplemented by a method of quantitative evaluation, enabling the competent authority to have the conformity of the medicinal product with its specification verified after it has been placed on the market.

An *in vivo* or *in vitro* biological assay shall be obligatory when physico-chemical methods cannot provide adequate information on the quality of the product. Such an assay shall, whenever possible, include reference materials and statistical analysis allowing calculation of confidence limits. Where these tests cannot be carried out on the finished product, they may be performed at an intermediate stage, as late as possible in the manufacturing process.

Where degradation occurs during manufacture of the finished product, the maximum acceptable levels of individual and total degradation products immediately following manufacture shall be indicated.

Where the particulars given in Section B show that a significant overage of an active substance is employed in the manufacture of the medicinal product or where the stability data show that the assay of the active substance declines on storage, the description of the control tests on the finished product shall include, where appropriate, the chemical and, if necessary, the toxico-pharmacological investigation of the changes that this substance has undergone, and possibly the characterisation and/or assay of the degradation products.

3. **Identification and assay of excipient components**

An identification test and an upper and lower limit test shall be obligatory for each individual antimicrobiological preservative and for any excipient that is liable to affect the bioavailability of the active substance, unless the bioavailability is guaranteed by other appropriate tests. An identification test and an upper limit test shall be obligatory for any antioxidant and for any excipient liable to adversely affect physiological functions, with a lower limit test also included for antioxidants at time of release.

4. **Safety tests**

Apart from the toxico-pharmacological tests submitted with the application for marketing authorisation, particulars of safety tests, such as sterility and bacterial endotoxins, shall be included in the analytical particulars wherever such tests must be undertaken as a matter of routine in order to verify the quality of the product.

F. STABILITY TEST

1. **Active substances(s)**

A retest period and storage conditions for the active substance shall be specified except in the case where the active substance is the subject of a monograph in the *European Pharmacopoeia* and the manufacturer of the finished product fully retests the active substance immediately before its use in the manufacture of the finished product.

Stability data shall be presented to support the defined retest period and storage conditions. The type of stability studies conducted, protocols used, the analytical procedures used and their validation together with the detailed results shall be presented. The stability commitment with a summary of the protocol shall be provided.

However, where a Certificate of Suitability for the active substance from the proposed source is available and specifies a retest period and storage conditions, stability data for the active substance from that source are not required.

2. **Finished product**

A description shall be given of the investigations by which the shelf life, the recommended storage conditions and the specifications at the end of the shelf life proposed by the applicant have been determined.

The type of stability studies conducted, protocols used, the analytical procedures used and their validation together with the detailed results shall be presented.

Where a finished product requires reconstitution or dilution prior to administration, details of the proposed shelf life and specification for the reconstituted/diluted product are required, supported by relevant stability data.

In the case of multi-dose containers, where relevant, stability data shall be presented to justify a shelf life for the product after it has been broached for the first time and an in-use specification shall be defined.

Where a finished product is liable to give rise to degradation products, the applicant shall declare these and indicate the identification methods and test procedures.

The conclusions shall contain the results of analyses, justifying the proposed shelf life and if appropriate, the in-use shelf life, under the recommended storage conditions and the specifications of the finished product at the end of the shelf life, and in-use shelf life if appropriate, of the finished product under these recommended storage conditions.

The maximum acceptable level of individual and total degradation products at the end of shelf life shall be indicated.

A study of the interaction between product and container shall be submitted wherever the risk of such interaction is regarded as possible, especially where injectable preparations are concerned.

The stability commitment with a summary of the protocol shall be provided.

G. OTHER INFORMATION

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

For medicated premixes (products intended for incorporation into medicated feedingstuffs), information shall be provided on inclusion rates, instructions for incorporation, homogeneity in-feed, compatibility/suitable feedingstuffs, stability in-feed, and the proposed in-feed shelf life. A specification for the medicated feedingstuffs, manufactured using these premixes in accordance with the recommended instructions for use shall also be provided.

PART 3: *SAFETY AND RESIDUES TESTS*

The particulars and documents which shall accompany the application for marketing authorisation pursuant to the second and fourth indents of Article 12(3)(j) shall be submitted in accordance with the requirements below.

A. ***Safety tests***

CHAPTER I: PERFORMANCE OF TESTS

The safety documentation shall show:

(a) the potential toxicity of the veterinary medicinal product and any dangerous or undesirable effects which may occur under the proposed conditions of use in animals; these should be evaluated in relation to the severity of the pathological condition concerned;

(b) the potential harmful effects to man of residues of the veterinary medicinal product or substance in foodstuffs obtained from treated animals and what difficulties these residues may create in the industrial processing of foodstuffs;

(c) the potential risks which may result from the exposure of human beings to the veterinary medicinal product, for example during its administration to the animal;

(d) the potential risks for the environment resulting from the use of the veterinary medicinal product.

All results shall be reliable and valid generally. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results. Additionally, information shall be provided regarding the therapeutic potential of the product and about the hazards connected with its use.

In some cases it may be necessary to test the metabolites of the parent compound where these represent the residues of concern.

An excipient used in the pharmaceutical field for the first time shall be treated like an active substance.

1. **Precise identification of the product and of its active substance(s)**

— international non-proprietary name (INN),

— International Union of Pure and Applied Chemistry Name (IUPAC),

— Chemical Abstract Service (CAS) number,

— therapeutic, pharmacological and chemical classification,

— synonyms and abbreviations,

— structural formula,

— molecular formula,

— molecular weight,

— degree of impurity,

— qualitative and quantitative composition of impurities,

— description of physical properties,

— melting point,

— boiling point,

— vapour pressure,

— solubility in water and organic solvents expressed in g/l, with indication of temperature,

— density,

— spectra of refraction, rotation, etc,

— formulation of the product.

2. **Pharmacology**

Pharmacological studies are of fundamental importance in clarifying the mechanisms by which the veterinary medicinal product produces its therapeutic effects and therefore pharmacological studies conducted in experimental and target species of animal shall be included in Part 4.

However, pharmacological studies may also assist in the understanding of toxicological phenomena. Moreover, where a veterinary medicinal product produces pharmacological effects in the absence of a toxic response, or at doses lower than those required to elicit toxicity, these pharmacological effects shall be taken into account during the evaluation of the safety of the veterinary medicinal product.

Therefore the safety documentation shall always be preceded by details of pharmacological investigations undertaken in laboratory animals and all relevant information observed during clinical studies in the target animal.

2.1. *Pharmacodynamics*

Information on the mechanism of action of the active substance(s) shall be provided, together with information on primary and secondary pharmacodynamic effects in order to assist in the understanding of any adverse effects in the animal studies.

2.2. *Pharmacokinetics*

Data on the fate of the active substance and its metabolites in the species used in the toxicological studies shall be provided, covering absorption, distribution, metabolism and excretion (ADME). The data shall be related to the dose/effect findings in the pharmacological and toxicological studies, to determine adequate exposure. Comparison with the pharmacokinetic data obtained in the studies on the target species, Part 4, Chapter I, Section A.2, shall be included in Part 4 in order to determine the relevance of the results obtained in the toxicology studies for the toxicity to the target species.

3. **Toxicology**

The documentation on toxicology shall follow the guidance published by the Agency on the general approach to testing and guidance on particular studies. This guidance includes:

1. basic tests required for all new veterinary medicinal products for use in food-producing animals in order to assess the safety of any residues present in food for human consumption;

2. additional tests that may be required depending on specific toxicological concerns such as those associated with the structure, class, and mode of action of the active substance(s);

3. special tests which might assist in the interpretation of data obtained in the basic or additional tests.

The studies shall be conducted with the active substance(s), not with the formulated product. Where studies of the formulated product are required, this is specified in the text below.

3.1. *Single-dose toxicity*

Single-dose toxicity studies may be used to predict:

— the possible effects of acute overdosage in the target species,

— the possible effects of accidental administration to humans,

— the doses which may usefully be employed in the repeat dose studies.

Single-dose toxicity studies should reveal the acute toxic effects of the substance and the time course for their onset and remission.

The studies to be carried out shall be selected with a view to providing information on user safety, e.g. if substantial exposure by inhalation or dermal contact of the user of the veterinary medicinal product is anticipated, those routes of exposure shall be studied.

3.2. *Repeat-dose toxicity*

Repeat-dose toxicity tests are intended to reveal any physiological and/or pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

In the case of pharmacologically active substances or veterinary medicinal products intended solely for use in non-food-producing animals, a repeat-dose toxicity study in one species of experimental animal shall normally be sufficient. This study may be replaced by a study conducted in the target animal. The frequency and route of administration, and the duration of the study shall be chosen having regard to the proposed conditions of clinical use. The investigator shall give his reasons for the extent and duration of the trials and the dosages chosen.

In the case of substances or veterinary medicinal products intended for use in food-producing animals, repeat-dose (90 day) toxicity testing shall be performed in a rodent and a non-rodent species in order to identify target organs and toxicological endpoints and identify the appropriate species and the dose levels to be used in chronic toxicity testing, if appropriate.

The investigator shall give his reasons for the choice of species, having regard to the available knowledge of the metabolism of the product in animals and man. The test substance shall be administered orally. The investigator shall clearly state and give his reasons for the method and frequency of administration and the length of the trials.

The maximum dose should normally be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity.

Evaluation of the toxic effects shall be based on observation of behaviour, growth, haematology and physiological tests, especially those relating to the excretory organs, and also on autopsy reports and accompanying histological data. The choice and range of each group of tests depends on the species of animal used and the state of scientific knowledge at the time.

In the case of new combinations of known substances which have been investigated in accordance with the provisions of this Directive, the repeat-dose tests may, except where toxicity tests have demonstrated potentiation or novel toxic effects, be suitably modified by the investigator, who shall submit his reasons for such modifications.

3.3. *Tolerance in the target species*

A summary shall be provided of any signs of intolerance which have been observed during studies conducted, usually with the final formulation, in the target species in accordance with the requirements of Part 4, Chapter I, Section B. The studies concerned, the dosages at which the intolerance occurred and the species and breeds concerned shall be identified. Details of any unexpected physiological changes shall also be provided. The full reports of these studies shall be included in Part 4.

3.4. *Reproductive toxicity including developmental toxicity*

3.4.1. Study of the effects on reproduction

The purpose of this study is to identify possible impairment of male or female reproductive function or harmful effects on progeny resulting from the administration of the veterinary medicinal products or substance under investigation.

In the case of pharmacologically active substances or veterinary medicinal products intended for use in food-producing animals, the study of the effects on reproduction shall be performed in the form of a multi-generation reproduction study, designed to detect any effect on mammalian reproduction. These include effects on male and female fertility, mating, conception, implantation, ability to maintain pregnancy to term, parturition, lactation, survival, growth and development of the offspring from birth through to weaning, sexual maturity and the subsequent reproductive function of the offspring as adults. At least three dose levels shall be used. The maximum dose should be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity.

3.4.2. Study of developmental toxicity

In the case of pharmacologically active substances or veterinary medicinal products intended for use in food-producing animals, tests on developmental toxicity shall be performed. These tests shall be designed to detect any adverse effects on the pregnant female and development of the embryo and foetus consequent to exposure of the female from implantation through gestation to the day before predicted birth. Such adverse effects include enhanced toxicity relative to that observed in non-pregnant females, embryo-foetal death, altered foetal growth, and structural changes to the foetus. A developmental toxicity test in the rat is required. Depending on the results, a study in a second species may have to be performed, in accordance with established guidance.

In the case of pharmacologically active substances or veterinary medicinal products not intended for use in food producing animals, a study of developmental toxicity shall be performed in at least one species, which may be the target species, if the product is intended for use in female animals which may be used for breeding. However, where the use of the veterinary medicinal product would result in significant exposure to users, standard developmental toxicity studies shall be performed.

3.5. *Genotoxicity*

Tests for genotoxic potential shall be performed to reveal changes which a substance may cause in the genetic material of cells. Any substance intended to be included in a veterinary medicinal product for the first time must be assessed for genotoxic properties.

A standard battery of *in vitro* and *in vivo* genotoxicity tests in accordance with established guidance shall usually be carried out on the active substance(s). In some cases, it may also be necessary to test one or more metabolites that occur as residues in foodstuffs.

3.6. *Carcinogenicity*

The decision on whether carcinogenicity testing is required shall take into account the results of genotoxicity tests, structure-activity relationships and the findings in systemic toxicity tests that may be relevant to neoplastic lesions in longer term studies.

Any known species specificity of the mechanism of toxicity shall be considered, as well as any differences in metabolism between the test species, target animal species, and human beings.

Where carcinogenicity testing is necessary, generally a two-year rat study and an 18-month mouse study are required. With appropriate scientific justification, carcinogenicity studies may be carried out in one rodent species, preferably the rat.

3.7. *Exceptions*

Where a veterinary medicinal product is intended for topical use, systemic absorption shall be investigated in the target animal species. If it is proved that systemic absorption is negligible, the repeated dose toxicity tests, the tests for reproductive toxicity and the carcinogenicity tests may be omitted, unless:

— under the intended conditions of use laid down, oral ingestion of the veterinary medicinal product by the animal is to be expected, or

— under the intended conditions of use laid down, exposure of the user of the veterinary medicinal product by other routes than the dermal route is to be expected, or

— the active substance or metabolites may enter foodstuffs obtained from the treated animal.

4. **Other requirements**

4.1. *Special studies*

For particular groups of substances or if the effects observed during repeated dose studies in animals include changes indicative of e.g. immunotoxicity, neurotoxicity- or, endocrine dysfunction, further testing shall be required, e.g. sensitisation studies or delayed neurotoxicity tests. Depending on the nature of the product, it may be necessary to conduct additional studies to assess the underlying mechanism of the toxic effect or the irritation potential. Such studies shall usually be conducted with the final formulation.

The state of scientific knowledge and established guidance shall be taken into account when designing such studies and evaluating their results.

4.2. *Microbiological properties of residues*

4.2.1. Potential effects on the human gut flora

The potential microbiological risk presented by residues of antimicrobial compounds for the human intestinal flora shall be investigated in accordance with established guidance.

4.2.2. Potential effects on the microorganisms used for industrial food processing

In certain cases, it may be necessary to carry out tests to determine whether microbiologically active residues may interfere in technological processes in the industrial processing of foodstuff.

4.3. *Observations in humans*

Information shall be provided showing whether the pharmacologically active substances of the veterinary medicinal product are used as medicinal products in human therapy; if this is so, a compilation shall be made of all the effects observed (including adverse reactions) in humans and of their cause, to the extent that they may be important for the assessment of the safety of the veterinary medicinal product, where appropriate including results from published studies; where constituents of the veterinary medicinal products are themselves not used or are no longer used as medicinal products in human therapy, the reasons shall be stated.

4.4. *Development of resistance*

Data on the potential emergence of resistant bacteria of relevance for human health are necessary in the case of veterinary medicinal products. The mechanism of the development of such resistance is particularly important in this regard. Where necessary, measures to limit resistance development from the intended use of the veterinary medicinal product shall be proposed.

Resistance relevant for clinical use of the product shall be addressed in accordance with Part 4. Where relevant, cross reference shall be made to the data set out in Part 4.

5. **User safety**

This section shall include a discussion of the effects found in the preceding sections and relate this to the type and extent of human exposure to the product with a view to formulating appropriate user warnings and other risk management measures.

6. **Environmental risk assessment**

6.1. *Environmental risk assessment of veterinary medicinal products not containing or consisting of genetically modified organisms*

An environmental risk assessment shall be performed to assess the potential harmful effects, which the use of the veterinary medicinal product may cause to the environment and to identify the risk of such effects. The assessment shall also identify any precautionary measures which may be necessary to reduce such risk.

This assessment shall normally be conducted in two phases. The first phase of the assessment shall always be performed. The details of the assessment shall be provided in accordance with accepted guidance. It shall indicate the potential exposure of the environment to the product and the level of risk associated with any such exposure taking into account in particular the following items:

— the target animal species, and the proposed pattern of use,

— the method of administration, in particular the likely extent to which the product will enter directly into environmental systems,

— the possible excretion of the product, its active substances or relevant metabolites into the environment by treated animals; persistence in such excreta,

— the disposal of unused veterinary medicinal product or other waste product.

In the second phase, further specific investigation of the fate and effects of the product on particular ecosystems shall be conducted, in accordance with established guidance. The extent of exposure of the product to the environment, and the available information about the physical/chemical, pharmacological and/or toxicological properties of the substance(s) concerned, including metabolites in case of an identified risk, which has been obtained during the conduct of the other tests and trials required by this Directive, shall be taken into consideration.

6.2. *Environmental risk assessment for veterinary medicinal products containing or consisting of genetically modified organisms*

In the case of a veterinary medicinal product containing or consisting of genetically modified organisms the application shall also be accompanied by the documents required under Article 2 and Part C of Directive 2001/18/EC.

CHAPTER II: PRESENTATION OF PARTICULARS AND DOCUMENTS

The dossier of safety tests shall include the following:

— an index of all studies included in the dossier,

— a statement confirming that all data known by the applicant at the time of submission, whether favourable or unfavourable, are included,

— a justification for the omission of any type of study,

— an explanation of the inclusion of an alternative type of study,

— a discussion of the contribution that any study that pre-dates studies performed in line with good laboratory practice (GLP) according to Directive 2004/10/EC can make to the overall risk assessment.

Each study report shall include:

— a copy of the study plan (protocol),

— a statement of compliance with good laboratory practice, where applicable,

— a description of the methods, apparatus and materials used,

— a description and justification of the test system,

— a description of the results obtained, in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author,

— a statistical analysis of the results where appropriate,

— a discussion of the results, with comment on observed and no-observed-effect levels, and on any unusual findings,

— a detailed description and a thorough discussion of the results of the study of the safety profile of the active substance, and its relevance for the evaluation of potential risks presented by residues to humans.

B. ***Residue tests***

CHAPTER I: PERFORMANCE OF TESTS

1. **Introduction**

For the purposes of this Annex, the definitions of Council Regulation (EEC) No 2377/90 [1] shall apply.

The purpose of studying the depletion of residues from the edible tissues or of eggs, milk and honey derived from treated animals is to determine under what conditions and to what extent residues may persist in foodstuffs produced from these animals. In addition, the studies shall enable the determination of a withdrawal period.

In the case of veterinary medicinal products intended for use in food-producing animals, the residue documentation shall show:

1. to what extent, and how long, do residues of the veterinary medicinal product or its metabolites persist in the edible tissues of the treated animal or in milk, eggs and/or honey obtained therefrom;

2. that in order to prevent any risk to the health of the consumer of foodstuffs from treated animals, or difficulties in the industrial processing of foodstuffs, it is possible to establish realistic withdrawal periods which can be observed under practical farming conditions;

3. that the analytical method(s) used in the residues depletion study are sufficiently validated to provide the necessary reassurance that the residues data submitted are suitable as the basis for a withdrawal period.

[1] OJ L 224, 18.8.1990, p. 1.

2. **Metabolism and residue kinetics**

2.1. *Pharmacokinetics (absorption, distribution, metabolism, excretion)*

A summary of the pharmacokinetic data shall be submitted with cross reference to the pharmacokinetic studies in target species submitted in Part 4. The full study report does not need to be submitted.

The purpose of pharmacokinetic studies with respect to residues of veterinary medicinal products is to evaluate the absorption, distribution, metabolism and excretion of the product in the target species.

The final product, or a formulation, which has comparable characteristics in terms of bioavailability as the final product, shall be administered to the target animal species at the maximum recommended dose.

Having regard to the method of administration, the extent of absorption of the veterinary medicinal product shall be fully described. If it is demonstrated that systemic absorption of products for topical application is negligible, further residue studies will not be required.

The distribution of the veterinary medicinal product in the target animal shall be described; the possibility of plasma protein binding or passage into milk or eggs and of the accumulation of lipophilic compounds shall be considered.

The pathways for the excretion of the product from the target animal shall be described. The major metabolites shall be identified and characterised.

2.2. *Depletion of residues*

The purpose of these studies, which measure the rate at which residues deplete in the target animal after the last administration of the medicinal product, is to permit the determination of withdrawal periods.

At a sufficient number of times after the test animal has received the final dose of the veterinary medicinal product, the quantities of residues present shall be determined by validated analytical methods; the technical procedures and the reliability and sensitivity of the methods employed shall be specified.

3. **Residue analytical method**

The analytical method(s) used in the residues depletion study (studies) and its (their) validation shall be described in detail.

The following characteristics shall be described:

— specificity,

— accuracy,

— precision,

— limit of detection,

— limit of quantification,

— practicability and applicability under normal laboratory conditions,

— susceptibility to interference,

— stability of incurred residues.

The suitability of the analytical method proposed shall be evaluated in the light of the state of scientific and technical knowledge at the time the application is submitted.

The analytical method shall be presented in an internationally agreed format.

CHAPTER II: PRESENTATION OF PARTICULARS AND DOCUMENTS

1. **Identification of the product**

An identification of the veterinary medicinal product(s) used in the testing shall be provided, including:

— composition,

— the physical and chemical (potency and purity) test results for the relevant batch(es),

— batch identification,

— relationship to the final product,

— specific activity and radio-purity of labelled substances,

— position of labelled atoms in the molecule.

The dossier of residue tests shall include:

— an index of all studies included in the dossier,

— a statement confirming that all data known by the applicant at the time of submission, whether favourable or unfavourable, are included,

— a justification for the omission of any type of study,

— an explanation of the inclusion of an alternative type of study,

— a discussion of the contribution that any study that pre-dates GLP can make to the overall risk assessment,

— a withdrawal period proposal.

Each study report shall include:

— a copy of the study plan (protocol),

— a statement of compliance with good laboratory practice, where applicable,

— a description of the methods, apparatus and materials used,

— a description of the results obtained, in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author,

— a statistical analysis of the results where appropriate,

— a discussion of the results,

— an objective discussion of the results obtained, and proposals concerning the withdrawal periods necessary to ensure that no residues which might constitute a hazard for consumers are present in foodstuffs obtained from treated animals.

PART 4: *PRE-CLINICAL AND CLINICAL TRIAL*

The particulars and documents, which shall accompany applications for marketing authorisations pursuant to the third indent of Article 12(3)(j) shall be submitted in accordance with the requirements below.

CHAPTER I: PRE-CLINICAL REQUIREMENTS

Pre-clinical studies are required to establish the pharmacological activity and the tolerance of the product.

A. **Pharmacology**

A.1. *Pharmacodynamics*

The pharmacodynamic effects of the active substance(s) included in the veterinary medicinal product shall be characterised.

First, the mechanism of action and the pharmacological effects on which the recommended application in practice is based shall be adequately described. The results shall be expressed in quantitative terms (using, for example, dose-effect curves, time-effect curves, etc.) and, wherever possible, in comparison with a substance the activity of which is well known. Where a higher efficacy is being claimed for an active substance, the difference shall be demonstrated and shown to be statistically significant.

Secondly, an overall pharmacological assessment of the active substance shall be provided, with special reference to the possibility of secondary pharmacological effects. In general, the effects on the main body functions shall be investigated.

Any effect of the other characteristics of the products (such as the route of administration or formulation) on the pharmacological activity of the active substance shall be investigated.

The investigations shall be intensified where the recommended dose approaches a dose likely to produce adverse reactions.

The experimental techniques, unless they are standard procedures, shall be described in such detail as to allow them to be reproduced, and the investigator shall establish their validity. The experimental results shall be set out clearly and, for certain types of tests, their statistical significance quoted.

Unless good reasons are given to the contrary, any quantitative modification of responses resulting from repeated administration of the substance shall also be investigated.

Fixed combinations may be prompted either on pharmacological grounds or by clinical indications. In the first case, the pharmacodynamic and/or pharmacokinetic studies shall demonstrate those interactions, which might make the combination itself of value in clinical use. In the second case, where scientific justification for the medicinal combination is sought through clinical experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals and, at least, the importance of any adverse reactions shall be checked. If a combination includes a new active substance, the latter shall have been previously studied in depth.

A.2. *Development of resistance*

Where relevant, data on the potential emergence of resistant organisms of clinical relevance are necessary for veterinary medicinal products. The mechanism of the development of such resistance is particularly important in this regard. Measures to limit resistance development from the intended use of the veterinary medicinal product shall be proposed by the applicant.

Where relevant, cross reference shall be made to data set out in Part 3.

A.3. *Pharmacokinetics*

Basic pharmacokinetic data concerning a new active substance are required in the context of assessment of the clinical safety and efficacy of the veterinary medicinal product.

The objectives of pharmacokinetic studies in the target animal species can be divided into three main areas:

(i) descriptive pharmacokinetics leading to the determination of basic parameters.;

(ii) use of these parameters to investigate the relationships between dosage regimen, plasma and tissue concentration over time and pharmacological, therapeutic or toxic effects;

(iii) where appropriate, to compare the kinetics between different target species and to explore possible species differences having an impact on target animal safety and efficacy of the veterinary medicinal product.

In the target animal species, pharmacokinetic studies are, as a rule, necessary as a complement to the pharmacodynamic studies to support the establishment of effective dosage regimens (route and site of administration, dose, dosing interval, number of administrations, etc.). Additional pharmacokinetic studies may be required to establish dosage regimens according to certain population variables.

Where pharmacokinetic studies have been submitted under Part 3 cross reference to such studies may be made.

In the case of new combinations of known substances which have been investigated in accordance with the provisions of this Directive, pharmacokinetic studies of the fixed combination are not required if it can be justified that the administration of the active substances as a fixed combination does not change their pharmacokinetic properties.

Appropriate bioavailability studies shall be undertaken to establish bioequivalence:

— when comparing a reformulated veterinary medicinal product with the existing one,

— where necessary for the comparison of a new method or route of administration with an established one.

B. **Tolerance in the target animal species**

The local and systemic tolerance of the veterinary medicinal product shall be investigated in the target animal species. The purpose of these studies is to characterise signs of intolerance and to establish an adequate margin of safety using the recommended route(s) of administration. This may be achieved by increasing the therapeutic dose and/or the duration of treatment. The report on the trials shall contain details of all expected pharmacological effects and all adverse reactions.

CHAPTER II: CLINICAL REQUIREMENTS

1. **General principles**

The purpose of clinical trials is to demonstrate or substantiate the effect of the veterinary medicinal product after administration at the proposed dosage regimen via the proposed route of administration and to specify its indications and contra-indications according to species, age, breed and sex, its directions for use as well as any adverse reactions which it may have.

Experimental data shall be confirmed by data obtained under normal field conditions.

Unless justified, clinical trials shall be carried out with control animals (controlled clinical trials). The efficacy results obtained should be compared with those from the target animal species that have received a veterinary medicinal product authorised in the Community for the same indications for use in the same target animal species, or a placebo or no treatment. All the results obtained, whether positive or negative, shall be reported.

Established statistical principles shall be used in protocol design, analysis and evaluation of clinical trials, unless justified.

In the case of a veterinary medicinal product intended primarily for use as a performance enhancer, particular attention shall be given to:

1. the yield of animal produce,

2. the quality of animal produce (organoleptic, nutritional, hygienic and technological qualities),

3. nutritional efficiency and growth of target animal species,

4. general health status of the target animal species.

2. **Conduct of clinical trials**

All veterinary clinical trials shall be conducted in accordance with a detailed trial protocol.

Clinical field trials shall be conducted in accordance with established principles of good clinical practice, unless otherwise justified.

Before the commencement of any field trial, the informed consent of the owner of the animals to be used in the trial shall be obtained and documented. In particular, the animal owner shall be informed in writing of the consequences of participation in the trial for the subsequent disposal of treated animals or for the taking of foodstuffs from treated animals. A copy of this notification, countersigned and dated by the animal owner, shall be included in the trial documentation.

Unless the field trial is conducted with a blind design, the provisions of Articles 55, 56 and 57 shall apply by analogy to the labelling of formulations intended for use in veterinary field trials. In all cases, the words "for veterinary field trial use only" shall appear prominently and indelibly upon the labelling.

CHAPTER III: PARTICULARS AND DOCUMENTS

The dossier on efficacy shall include all pre-clinical and clinical documentation and/or results of trials, whether favourable or unfavourable to the veterinary medicinal products, in order to enable an objective overall assessment of the risk/benefit balance of the product.

1. **Results of pre-clinical trials**

Wherever possible, particulars shall be given of the results of:

(a) tests demonstrating pharmacological actions;

(b) tests demonstrating the pharmacodynamic mechanisms underlying the therapeutic effect;

(c) tests demonstrating the main pharmacokinetic profile;

(d) tests demonstrating target animal safety;

(e) tests investigating resistance.

Should unexpected results occur during the course of the tests, these should be detailed.

Additionally, the following particulars shall be provided in all pre-clinical studies:

(a) a summary;

(b) a detailed experimental protocol giving a description of the methods, apparatus and materials used, details such as species, age, weight, sex, number, breed or strain of animals, identification of animals, dose, route and schedule of administration;

(c) a statistical analysis of the results, where relevant;

(d) an objective discussion of the results obtained, leading to conclusions on the efficacy and safety of the veterinary medicinal product.

Total or partial omission of any of these data shall be justified.

2. **Results of clinical trials**

All the particulars shall be supplied by each of the investigators on individual record sheets in the case of individual treatment and collective record sheets in the case of collective treatment.

The particulars supplied shall take the following form:

(a) name, address, function and qualifications of investigator in charge;

(b) place and date of treatment; name and address of owner of the animals;

(c) details of the clinical trial protocol giving a description of the methods used, including methods of randomisation and blinding, details such as the route of administration, schedule of administration, the dose, identification of trial animals, species, breeds or strains, age, weight, sex, physiological status;

(d) method of animal management and feeding, stating the composition of the feed and the nature and quantity of any feed additives;

(e) case history (as full as possible), including occurrence and course of any intercurrent diseases;

(f) diagnosis and means used to make it;

(g) clinical signs, if possible according to conventional criteria;

(h) precise identification of the formulation of the veterinary medicinal product used in the clinical trial and the physical and chemical test results for the relevant batch(es);

(i) dosage of the veterinary medicinal product, method, route and frequency of administration and precautions, if any, taken during administration (duration of injection, etc.);

(j) duration of treatment and period of subsequent observation;

(k) all details concerning other veterinary medicinal products which have been administered during the period of examination, either prior to or concurrently with the test product and, in the latter case, details of any interactions observed;

(l) all results of the clinical trials, fully describing the results based on the efficacy criteria and end points specified in the clinical trial protocol and including the results of the statistical analyses, if appropriate;

(m) all particulars of any unintended event, whether harmful or not, and of any measures taken in consequence; the cause-and-effect relationship shall be investigated if possible;

(n) effect on animals' performance if appropriate;

(o) effects on the quality of foodstuffs obtained from treated animals, particularly in the case of veterinary medicinal products intended for use as performance enhancers;

(p) a conclusion on the safety and efficacy in each individual case or, summarised in terms of frequencies or other appropriate variables where specific mass treatment is concerned.

Omission of one or more items (a) to (p) shall be justified.

The marketing authorisation holder shall make all necessary arrangements to ensure that the original documents, which formed the basis of the data supplied, are kept for at least five years after the veterinary medicinal product is no longer authorised.

In respect of each clinical trial, the clinical observations shall be summarised in a synopsis of the trials and the results thereof, indicating in particular:

(a) the number of control and test animals treated either individually or collectively, with a breakdown according to species, breed or strain, age and sex;

(b) the number of animals withdrawn prematurely from the trials and the reasons for such withdrawal;

(c) in the case of control animals, whether they have:

— received no treatment, or

— received a placebo, or

— received another veterinary medicinal product authorised in the Community for the same indication for use in the same target animal species, or

— received the same active substance under investigation in a different formulation or by a different route;

(d) the frequency of observed adverse reactions;

(e) observations as to the effect on animal performance, if appropriate;

(f) details concerning test animals which may be at increased risk owing to their age, their mode of rearing or feeding, or the purpose for which they are intended, or animals the physiological or pathological condition of which requires special consideration;

(g) a statistical evaluation of the results.

Finally, the investigator shall draw general conclusions on the efficacy and safety of the veterinary medicinal product under the proposed conditions of use, and in particular any information relating to indications and contraindications, dosage and average duration of treatment and where, appropriate, any interactions observed with other veterinary medicinal products or feed additives as well as any special precautions to be taken during treatment and the clinical symptoms of overdosage, when observed.

In the case of fixed combination products, the investigator shall also draw conclusions concerning the safety and the efficacy of the product when compared with the separate administration of the active substances involved.

TITLE II

REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Without prejudice to specific requirements laid down by Community legislation for the control and eradication of specific infectious animal diseases, the following requirements shall apply to immunological veterinary medicinal products, except when the products are intended for use in some species or with specific indications as defined in Title III and in relevant guidelines.

PART 1: *SUMMARY OF THE DOSSIER*

A. ADMINISTRATIVE INFORMATION

The immunological veterinary medicinal product, which is the subject of the application, shall be identified by name and by name of the active substance(s), together with the biological activity, potency or titre, the pharmaceutical form, the route and method if appropriate of administration and a description of the final presentation of the product, including packaging, labelling and leaflet. Diluents may be packed together with the vaccine vials or separately.

Information on diluents needed for making the final vaccine preparation shall be included in the dossier. An immunological veterinary medicinal product is regarded as one product even when more than one diluent is required so that different preparations of the final product can be prepared, which may be for administration by different routes or methods of administration.

The name and address of the applicant shall be given, together with the name and address of the manufacturer and the sites involved in the different stages of manufacture and control (including the manufacturer of the finished product and the manufacturer(s) of the active substance(s)) and where relevant the name and address of the importer.

The applicant shall identify the number and titles of volumes of documentation submitted in support of the application and indicate what samples, if any, are also provided.

Annexed to the administrative information shall be copies of a document showing that the manufacturer is authorised to produce immunological veterinary medicinal products, as defined in Article 44. Moreover, the list of organisms handled at the production site shall be given.

The applicant shall submit a list of countries in which authorisation has been granted, and a list of countries in which an application has been submitted or refused.

B. SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The applicant shall propose a summary of the product characteristics, in accordance with Article 14.

A proposed labelling text for the immediate and outer packaging shall be provided in accordance with Title V of this Directive, together with a package leaflet where one is required pursuant to Article 61. In addition the applicant shall provide one or more specimens or mock-ups of the final presentation(s) of the veterinary medicinal product in at least one of the official languages of the European Union; the mock-up may be provided in black and white and electronically where prior agreement from the competent authority has been obtained.

C. DETAILED AND CRITICAL SUMMARIES

Each detailed and critical summary referred to in the second subparagraph of Article 12(3) shall be prepared in the light of the state of scientific knowledge at the time of submission of the application. It shall contain an evaluation of the various tests and trials, which constitute the marketing authorisation dossier and shall address all points relevant to the assessment of the quality, safety and efficacy of the immunological veterinary medicinal product. It shall give the detailed results of the tests and trials submitted and precise bibliographic references.

All important data shall be summarised in an appendix to the detailed and critical summaries, whenever possible in tabular or graphic form. The detailed and critical summaries shall contain precise cross references to the information contained in the main documentation.

The detailed and critical summaries shall be signed and dated, and information about the author's educational background, training and occupational experience shall be attached. The professional relationship of the author with the applicant shall be declared.

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.

PART 3: *SAFETY TESTS*

A. INTRODUCTION AND GENERAL REQUIREMENTS

The safety tests shall show the potential risks from the immunological veterinary medicinal product, which may occur under the proposed conditions of use in animals: these shall be evaluated in relation to the potential benefits of the product.

Where immunological veterinary medicinal products consist of live organisms, especially those, which could be shed by vaccinated animals, the potential risk to unvaccinated animals of the same or of any other potentially exposed species shall be evaluated.

The safety studies shall be carried out in the target species. The dose to be used shall be the quantity of the product to be recommended for use and the batch used for safety testing shall be taken from a batch or batches produced according to the manufacturing process described in Part 2 of the application.

In the case of an immunological veterinary medicinal products containing a live organism, the dose to be used in the laboratory tests described in Sections B.1 and B.2 shall be the quantity of the product containing the maximum titre. If necessary the concentration of the antigen may be adjusted to achieve the required dose. For inactivated vaccines the dose to be used shall be that quantity recommended for use containing the maximum antigen content unless justified.

The safety documentation shall be used for assessment of the potential risks which may result from the exposure of human beings to the veterinary medicinal product, for example during its administration to the animal.

B. LABORATORY TESTS

1. **Safety of the administration of one dose**

The immunological veterinary medicinal product shall be administered at the recommended dose and by each recommended route of administration to animals of each species and category in which it is intended for use, including animals of the minimum age of administration. The animals shall be observed and examined for signs of systemic and local reactions. Where appropriate, these studies shall include detailed post-mortem macroscopic and microscopic examinations of the injection site. Other objective criteria shall be recorded, such as rectal temperature and performance measurements.

The animals shall be observed and examined until reactions may no longer be expected, but in all cases, the observation and examination period shall be at least 14 days after administration.

This study may be part of the repeated dose study required under point 3 or omitted if the results of the overdose study required under point 2 have revealed no signs of systemic or local reactions.

2. **Safety of one administration of an overdose**

Only live immunological veterinary medicinal products require overdose testing.

An overdose of the immunological veterinary medicinal product shall be administered by each recommended route(s) of administration to animals of the most sensitive categories of the target species, unless the selection of the most sensitive of several similar routes is justified. In the case of immunological veterinary medicinal products administered by injection, the doses and route(s) of administration shall be chosen to take account of the maximum volume, which can be administered at any one single injection site. The animals shall be observed and examined for at least 14 days after administration for signs of systemic and local reactions. Other criteria shall be recorded, such as rectal temperature and performance measurements.

Where appropriate, these studies shall include detailed post-mortem macroscopic and microscopic examinations of the injection site if this has not been done under point 1.

3. **Safety of the repeated administration of one dose**

In the case of immunological veterinary medicinal products to be administered more than once, as part of the basic vaccination scheme, a study of the repeated administration of one dose shall be required to reveal any adverse effects induced by such administration. These tests shall be carried out on the most sensitive categories of the target species (such as certain breeds, age groups), using each recommended route of administration.

The animals shall be observed and examined for at least 14 days after the last administration for signs of systemic and local reactions. Other objective criteria shall be recorded, such as rectal temperature and performance measurements.

4. **Examination of reproductive performance**

Examination of reproductive performance shall be considered when data suggest that the starting material from which the product is derived may be a potential risk factor. Reproductive performance of males and non-pregnant and pregnant females shall be investigated with the recommended dose and by the most sensitive route of administration. In addition, harmful effects on the progeny, as well as teratogenic and abortifacient effects, shall be investigated.

These studies may form part of the safety studies described in points 1, 2, 3 or of the field studies provided for in Section C.

5. **Examination of immunological functions**

Where the immunological veterinary medicinal product might adversely affect the immune response of the vaccinated animal or of its progeny, suitable tests on the immunological functions shall be carried out.

6. **Special requirements for live vaccines**

6.1. *Spread of the vaccine strain*

Spread of the vaccine strain from vaccinated to unvaccinated target animals shall be investigated, using the recommended route of administration most likely to result in the spread. Moreover, it may be necessary to investigate the spread to non-target animal species which could be highly susceptible to a live vaccine strain.

6.2. *Dissemination in the vaccinated animal*

Faeces, urine, milk, eggs, oral, nasal and other secretions shall be tested for the presence of the organism as appropriate. Moreover, studies may be required of the dissemination of the vaccine strain in the body, with particular attention being paid to the predilection sites for replication of the organism. In the case of live vaccines for zoonoses within the meaning of Directive 2003/99/EC of the European Parliament and of the Council [1] to be used for food producing animals, these studies must shall take particularly into account the persistence of the organism at the injection site.

6.3. *Reversion to virulence of attenuated vaccines*

Reversion to virulence shall be investigated with the master seed. If the master seed is not available in sufficient quantity the lowest passage seed used for the production shall be examined. Use of another passage option shall be justified. The initial vaccination shall be carried out using the route of administration most likely to lead to reversion to virulence. Serial passages shall be made in target animals through five groups of animals, unless there is justification to make more passages or the organism disappears from the test animals sooner. Where the organism fails to replicate adequately, as many passages as possible shall be carried out in the target species.

6.4. *Biological properties of the vaccine strain*

Other tests may be necessary to determine as precisely as possible the intrinsic biological properties of the vaccine strain (e.g. neurotropism).

6.5. *Recombination or genomic reassortment of strains*

The probability of recombination or genomic reassortment with field or other strains shall be discussed.

7. **User safety**

This section shall include a discussion of the effects found in the preceding sections, which shall relate those effects to the type and extent of human exposure to the product with a view to formulating appropriate user warnings and other risk management measures.

[1] OJ L 325, 12.12.2003, p. 31.

8. **Study of residues**

For immunological veterinary medicinal products, it will normally not be necessary to undertake a study of residues. However, where adjuvants and/or preservatives are used in the manufacture of immunological veterinary medicinal products, consideration shall be given to the possibility of any residue remaining in the foodstuffs. If necessary, the effects of such residues shall be investigated.

A proposal for a withdrawal period shall be made and its adequacy shall be discussed in relation to any residue studies which have been undertaken.

9. **Interactions**

If there is a compatibility statement with other veterinary immunological products in the summary of product characteristics the safety of the association shall be investigated. Any other known interactions with veterinary medicinal products shall be described.

C. FIELD STUDIES

Unless justified, results from laboratory studies shall be supplemented with data from field studies, using batches according to the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same field studies.

D. ENVIRONMENTAL RISK ASSESSMENT

The purpose of the environmental risk assessment is to assess the potential harmful effects, which the use of the product may cause to the environment and to identify any precautionary measures, which may be necessary to reduce such risks.

This assessment shall normally be conducted in two phases. The first phase of the assessment shall always be performed. The details of the assessment shall be provided in accordance with established guidance. It shall indicate the potential exposure of the environment to the product and the level of risk associated with any such exposure, taking into account in particular the following items:

— the target animal species and the proposed pattern of use,

— the method of administration, in particular the likely extent to which the product will enter directly into the environmental system,

— the possible excretion of the product, its active substances into the environment by treated animals, persistence in such excreta,

— the disposal of unused or waste product.

In the case of live vaccine strains which may be zoonotic, the risk to humans shall be assessed.

Where the conclusions of the first phase indicate potential exposure of the environment to the product, the applicant shall proceed to the second phase and evaluate the potential risk(s) that the veterinary medicinal product might pose to the environment. Where necessary, further investigations on the impact of the product (soil, water, air, aquatic systems, non-target organisms) shall be carried out.

E. ASSESSMENT REQUIRED FOR VETERINARY MEDICINAL PRODUCTS CONTAINING OR CONSISTING OF GENETICALLY MODIFIED ORGANISMS

In the case of veterinary medicinal products containing or consisting of genetically modified organisms the application shall also be accompanied by the documents required under Article 2 and Part C of Directive 2001/18/EC.

PART 4: *EFFICACY TESTS*

CHAPTER I

1. **General principles**

The purpose of the trials described in this Part is to demonstrate or to confirm the efficacy of the immunological veterinary medicinal product. All claims made by the applicant with regard to the properties, effects and use of the product, shall be fully supported by results of specific trials contained in the application for marketing authorisation.

2. **Performance of trials**

All efficacy trials shall be conducted in accordance with a fully considered detailed protocol, which shall be recorded in writing prior to commencement of the trial. The welfare of the trial animals shall be subject to veterinary supervision and shall be taken fully into consideration during the elaboration of any trial protocol and throughout the conduct of the trial.

Pre-established systematic written procedures for the organisation, conduct, data collection, documentation and verification of efficacy trials shall be required.

Field trials shall be conducted in accordance with established principles of good clinical practice, unless otherwise justified.

Before the commencement of any field trial, the informed consent of the owner of the animals to be used in the trial shall be obtained and documented. In particular, the animal owner shall be informed in writing of the consequences of participation in the trial for the subsequent disposal of treated animals or for the taking of foodstuffs from treated animals. A copy of this notification, countersigned and dated by the animal owner, shall be included in the trial documentation.

Unless the field trial is conducted with a blind design, the provisions of Articles 55, 56 and 57 shall apply by analogy to the labelling of formulations intended for use in veterinary field trials. In all cases, the words "for veterinary field trial use only" shall appear prominently and indelibly upon the labelling.

CHAPTER II

A. **General requirements**

1. The choice of antigens or vaccine strains shall be justified on the basis of epizoological data.

2. Efficacy trials carried out in the laboratory shall be controlled trials, including untreated control animals unless this is not justified for animal welfare reasons and efficacy can be otherwise demonstrated.

In general, these laboratory trials shall be supported by trials carried out in field conditions, including untreated control animals.

All trials shall be described in sufficiently precise details so as to be reproducible in controlled trials, carried out at the request of the competent authorities. The investigator shall demonstrate the validity of all the techniques involved.

All results obtained, whether favourable or unfavourable, shall be reported.

3. The efficacy of an immunological veterinary medicinal product shall be demonstrated for each category of target animal species recommended for vaccination, by each recommended route of administration and using the proposed schedule of administration. The influence of passively acquired and maternally derived antibodies on the efficacy of a vaccine shall be adequately evaluated, if appropriate. Unless justified, the onset and duration of immunity shall be established and supported by data from trials.

4. The efficacy of each of the components of multivalent and combined immunological veterinary medicinal products shall be demonstrated. If the product is recommended for administration in combination with or at the same time as another veterinary medicinal product, they shall be shown to be compatible.

5. Whenever a product forms part of a vaccination scheme recommended by the applicant, the priming or booster effect or the contribution of the veterinary immunological product to the efficacy of the scheme as a whole shall be demonstrated.

6. The dose to be used shall be the quantity of the product to be recommended for use and the batch used for efficacy testing shall be taken from a batch or batches produced according to the manufacturing process described in Part 2 of the application.

7. If there is a compatibility statement with other immunological products in the summary of product characteristics, the efficacy of the association shall be investigated. Any other known interactions with any other veterinary medicinal products shall be described. Concurrent or simultaneous use may be allowed if supported by appropriate studies.

8. For diagnostic immunological veterinary medicinal products administered to animals, the applicant shall indicate how reactions to the product are to be interpreted.

9. For vaccines intended to allow a distinction between vaccinated and infected animals (marker vaccines), where the efficacy claim is reliant on *in vitro* diagnostic tests, sufficient data on the diagnostic tests shall be provided to allow adequate assessment of the claims related to the marker properties.

B. **Laboratory trials**

1. In principle, demonstration of efficacy shall be undertaken under well-controlled laboratory conditions by challenge after administration of the immunological veterinary medicinal product to the target animal under the recommended conditions of use. Insofar as possible, the conditions under which the challenge is carried out shall mimic the natural conditions for infection. Details of the challenge strain and its relevance shall be provided.

   For live vaccines, batches containing the minimum titre or potency shall be used unless justified. For other products, batches containing the minimum active content shall be used unless otherwise justified.

2. If possible, the immune mechanism (cell-mediated/humoral, local/general classes of immunoglobulin) which is initiated after the administration of the immunological veterinary medicinal product to target animals by the recommended route of administration shall be specified and documented.

C. **Field trials**

1. Unless justified, results from laboratory trials shall be supplemented with data from field trials, using batches representative of the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same field study.

2. Where laboratory trials cannot be supportive of efficacy, the performance of field trials alone may be acceptable.

PART 5: *PARTICULARS AND DOCUMENTS*

A. INTRODUCTION

The dossier of the safety and efficacy studies shall include an introduction defining the subject and indicating the tests which have been carried out in compliance with Parts 3 and 4 as well as a summary, with detailed references to the published literature. This summary shall contain an objective discussion of all the results obtained and lead to a conclusion on the safety and efficacy of the immunological veterinary medicinal product. Omission of any tests or trials listed shall be indicated and discussed.

B. LABORATORY STUDIES

The following shall be provided for all studies:

1. a summary;

2. the name of the body having carried out the studies;

3. a detailed experimental protocol giving a description of the methods, apparatus and materials used, details such as species or breed of animals, categories of animals, where they were obtained, their identification and number, the conditions under which they were housed and fed (stating, inter alia, whether they were free from any specified pathogens and/or specified antibodies, the nature and quantity of any additives contained in the feed), dose, route, schedule and dates of administration, a description and a justification of the statistical methods used;

4. in the case of control animals, whether they received a placebo or no treatment;

5. in the case of treated animals and where appropriate, whether they received the test product or another product authorised in the Community

6. all general and individual observations and results obtained (with averages and standard deviations), whether favourable or unfavourable. The data shall be described in sufficient detail to allow the results to be critically evaluated independently of their interpretation by the author. The raw data shall be presented in tabular form. By way of explanation and illustration, the results may be accompanied by reproductions of recordings, photomicrographs, etc;

7. the nature, frequency and duration of observed adverse reactions;

8. the number of animals withdrawn prematurely from the studies and reasons for such withdrawal;

9. a statistical analysis of the results, where such is called for by the test programme, and variance within the data;

10. occurrence and course of any intercurrent disease;

11. all details concerning veterinary medicinal products (other than the product under study), the administration of which was necessary during the course of the study;

12. an objective discussion of the results obtained, leading to conclusions on the safety and efficacy of the product.

C. FIELD STUDIES

Particulars concerning field studies shall be sufficiently detailed to enable an objective judgement to be made. They shall include the following:

1. a summary;

2. name, address, function and qualifications of the investigator in charge;

3. place and date of administration, identity code that can be linked to the name and address of the owner of the animal(s);

4. details of the trial protocol, giving a description of the methods, apparatus and materials used, details such as the route of administration, the schedule of administration, the dose, the categories of animals, the duration of observation, the serological response and other investigations carried out on the animals after administration;

5. in the case of control animals, whether they received a placebo or no treatment;

6. identification of the treated and control animals (collective or individual, as appropriate), such as species, breeds or strains, age, weight, sex, physiological status;

7. a brief description of the method of rearing and feeding, stating the nature and quantity of any additives contained in the feed;

8. all the particulars on observations, performances and results (with averages and standard deviation); individual data shall be indicated when tests and measurements on individuals have been carried out;

9. all observations and results of the studies, whether favourable or unfavourable, with a full statement of the observations and the results of the objective tests of activity required to evaluate the product; the techniques used must be specified and the significance of any variations in the results explained;

10. effects on the animals' performance;

11. the number of animals withdrawn prematurely from the studies and reasons for such withdrawal;

12. the nature, frequency and duration of observed adverse reactions;

13. occurrence and course of any intercurrent disease;

14. all details concerning veterinary medicinal products (other than the product under study) which have been administered either prior to or concurrently with the test product or during the observation period; details of any interactions observed;

15. an objective discussion of the results obtained, leading to conclusions on the safety and efficacy of the product.

PART 6: *BIBLIOGRAPHICAL REFERENCES*

The bibliographical references cited in the summary mentioned under Part 1 shall be listed in detail and copies shall be provided.

TITLE III

REQUIREMENTS FOR SPECIFIC MARKETING AUTHORISATION APPLICATIONS

1. **Generic veterinary medicinal products**

Applications based on Article 13 (generic veterinary medicinal products) shall contain the data referred to in Parts 1 and 2 of Title I of this Annex together with an environmental risk assessment and data demonstrating that the product has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product and data showing bio-equivalence with the reference medicinal product. If the reference veterinary medicinal product is a biological medicinal product, the documentation requirements in Section 2 for similar biological veterinary medicinal products shall be fulfilled.

For generic veterinary medicinal products the detailed and critical summaries on safety and efficacy shall particularly focus on the following elements:

— the grounds for claiming essential similarity,

— a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed together with an evaluation of these impurities,

— an evaluation of the bio-equivalence studies or a justification as to why studies were not performed with reference to established guidance,

— if applicable, additional data in order to demonstrate the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorised active substance shall be provided by the applicant; those data shall include evidence that there is no change in the pharmacokinetic or pharmacodynamic properties of the therapeutic moiety and/or in toxicity, which could influence the safety/efficacy profile.

Every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non-clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.

For generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided:

— evidence to demonstrate equivalent or differing depletion of residues from the administration site, which may be substantiated by appropriate residue depletion studies,

— evidence to demonstrate target animal tolerance at the administration site, which may be substantiated by appropriate target animal tolerance studies.

2. **Similar biological veterinary medicinal products**

In accordance with Article 13(4), where a biological veterinary medicinal product which is similar to a reference biological veterinary medicinal product does not meet the conditions in the definition of generic medicinal product, information to be supplied shall not be limited to Parts 1 and 2 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bioavailability data. In such cases, additional data shall be provided, in particular on the safety and efficacy of the product.

— The type and amount of additional data (i.e. toxicological and other safety studies and appropriate clinical studies) shall be determined on a case-by-case basis in accordance with relevant scientific guidelines.

— Due to the diversity of biological veterinary medicinal products, the competent authority shall determine the necessary studies foreseen in Parts 3 and 4, taking into account the specific characteristic of each individual biological veterinary medicinal product.

The general principles to be applied shall be addressed in guideline which shall be adopted by the Agency, taking into account the characteristics of the concerned biological veterinary medicinal product. If the reference biological veterinary medicinal product has more than one indication, the efficacy and safety of the biological veterinary medicinal product claimed to be similar shall be justified or, if necessary, demonstrated separately for each of the claimed indications.

3. **Well-established veterinary use**

For veterinary medicinal products the active substance(s) of which has/have been in "well-established veterinary use" as referred to in Article 13a, with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.

The applicant shall submit Parts 1 and 2 as described in Title I of this Annex.

For Parts 3 and 4, a detailed scientific bibliography shall address all aspects of the safety and efficacy.

The following specific rules shall apply in order to demonstrate the well-established veterinary use:

3.1. The following factors shall be taken into account in order to establish a well-established veterinary medicinal use of constituents of veterinary medicinal products:

(a) the time over which an active substance has been used;

(b) quantitative aspects of the use of the active substance;

(c) the degree of scientific interest in the use of the active substance (reflected in the published scientific literature);

(d) the coherence of scientific assessments.

Different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well-established veterinary use of a constituent of a medicinal product shall not be less than ten years from the first systematic and documented use of that substance as a veterinary medicinal product in the Community.

3.2. The documentation submitted by the applicant shall cover all aspects of the safety and/or efficacy assessment of the product for the proposed indication in the target species using the proposed route of administration and dosage regimen. It must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, shall be communicated. With respect to the provisions on well-established veterinary use, it is in particular necessary to clarify that bibliographic reference to other sources of evidence (post-marketing studies, epidemiological studies etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.

3.3. Particular attention must be paid to any missing information and justification must be given as to why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking.

3.4. The detailed and critical summaries regarding safety and efficacy must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether or not the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.

3.5. Post-marketing experience with other products containing the same constituents is of particular importance and applicants shall put a special emphasis on this issue.

4. **Combination veterinary medicinal products**

For applications based on Article 13b, a dossier containing Parts 1, 2, 3 and 4 shall be provided for the combination veterinary medicinal product. It shall not be necessary to provide studies on the safety and efficacy of each active substance. It shall nevertheless be possible to include information on the individual substances in the application for a fixed combination. The submission of data on each individual active substance, in conjunction with the required user safety studies, residues depletion studies and clinical studies on the fixed combination product, may be considered a suitable justification for omitting data on the combination product, based on animal welfare grounds and unnecessary testing on animals, unless there is suspected interaction leading to added toxicity. Where applicable, information regarding the manufacturing sites and the safety evaluation of adventitious agents shall be provided.

5. **Informed consent applications**

Applications based on Article 13c shall contain the data described in Part 1 of Title 1 of this Annex, provided that the marketing authorisation holder for the original veterinary medicinal product has given the applicant his consent to refer to the content of Parts 2, 3 and 4 of the dossier of that product. In this case, there is no need to submit quality, safety and efficacy detailed and critical summaries.

6. **Documentation for applications in exceptional circumstances**

A marketing authorisation may be granted subject to certain specific obligations requiring the applicant to introduce specific procedures, in particular concerning the safety and efficacy of the veterinary medicinal product, when, as provided for in Article 26(3) of this Directive, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use.

The identification of essential requirements for all applications mentioned in this section should be subject to guidelines which shall be adopted by the Agency.

7. **Mixed marketing authorisation applications**

Mixed marketing authorisation applications are applications where Part(s) 3 and/or 4 of the dossier consist of safety and efficacy studies carried out by the applicant as well as bibliographical references. All other part(s) are in accordance with the structure described in Part I of Title I of this Annex. The competent authority shall accept the proposed format presented by the applicant on a case-by-case basis.

TITLE IV

REQUIREMENTS FOR MARKETING AUTHORISATION APPLICATIONS FOR PARTICULAR VETERINARY MEDICINAL PRODUCTS

This part lays down specific requirements for identified veterinary medicinal products related to the nature of the active substances contained therein.

1. *IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS*

A. VACCINE ANTIGEN MASTER FILE

For particular immunological veterinary medicinal products and by derogation from the provisions of Title II, Part 2 Section C on active substances, the concept of a Vaccine Antigen Master File is introduced.

For the purpose of this Annex, a Vaccine Antigen Master File means a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information on quality concerning each of the active substances, which are part of this veterinary medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.

Scientific guidelines for the submission and evaluation of a vaccine antigen master file shall be adopted by the Agency. The procedure for the submission and evaluation of a vaccine antigen master file shall follow the guidance published by the Commission in *The rules governing medicinal products in the European Union*, Volume 6B, Notice to Applicants.

B. MULTI-STRAIN DOSSIER

For certain immunological veterinary medicinal products (foot-and-mouth disease, avian influenza and bluetongue) and by derogation from the provisions of Title II, Part 2 Section C on active substances the concept of the use of a multi-strain dossier is introduced.

A multi-strain dossier means a single dossier containing the relevant data for a unique and thorough scientific assessment of the different options of strains/combinations of strains permitting the authorisation of vaccines against antigenically variable viruses.

Scientific guidelines for the submission and evaluation of multi-strain dossiers shall be adopted by the Agency. The procedure for the submission and evaluation of multi-strain dossiers shall follow the guidance published by the Commission in *The rules governing medicinal products in the European Union*, Volume 6B, Notice to Applicants.

2. *HOMEOPATHIC VETERINARY MEDICINAL PRODUCTS*

This section sets out specific provisions on the application of Title I, Parts 2 and 3 to homeopathic veterinary medicinal products as defined in Article 1(8).

Part 2

The provisions of Part 2 shall apply to the documents submitted in accordance with Article 18 in the simplified registration of homeopathic veterinary medicinal products referred to in Article 17(1) as well as to the documents for authorisation of other homeopathic veterinary medicinal products referred to in Article 19(1) with the following modifications.

(a) *Terminology*

The Latin name of the homeopathic stock described in the marketing authorisation application dossier shall be in accordance with the Latin title of the *European Pharmacopoeia* or, in absence thereof, of an official pharmacopoeia of a Member State. Where relevant the traditional name(s) used in each Member State shall be provided.

(b) *Control of starting materials*

The particulars and documents on the starting materials, i.e. all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished homeopathic veterinary medicinal product, accompanying the application shall be supplemented by additional data on the homeopathic stock.

The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished homeopathic product. Where a toxic component is present, this should be controlled if possible in the final dilution. However, if this is not possible because of the high dilution, the toxic component shall normally be controlled at an earlier stage. Every step of the manufacturing process from the starting materials up to the final dilution to be incorporated into the finished product must be fully described.

In case dilutions are involved, these dilution steps shall be done in accordance with the homeopathic manufacturing methods laid down in the relevant monograph of the *European Pharmacopoeia* or, in absence thereof, in an official pharmacopoeia of a Member State.

(c) *Control tests on the finished medicinal product*

The general quality requirements shall apply to the homeopathic finished veterinary medicinal products. Any exception shall be duly justified by the applicant.

Identification and assay of all the toxicologically relevant constituents shall be carried out. If it can be justified that identification and/or an assay on all the toxicologically relevant constituents is not possible e.g. due to their dilution in the finished medicinal product the quality shall be demonstrated by complete validation of the manufacturing and dilution process.

(d) *Stability tests*

The stability of the finished product shall be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/potentisations obtained thereof. If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.

Part 3

The provisions of Part 3 shall apply to the simplified registration of homeopathic veterinary medicinal products referred to in Article 17(1) of this Directive with the following specification, without prejudice to the provisions of Regulation (EEC) No 2377/90 for substances included in the homeopathic stocks intended for administration to food-producing animal species.

Any missing information must be justified, e.g. justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.'

COMMISSION DIRECTIVE 2009/10/EC

of 13 February 2009

amending Directive 2008/84/EC laying down specific purity criteria on food additives other than colours and sweeteners

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 89/107/EEC of 21 December 1988 on the approximation of the laws of the Member States concerning food additives authorised for use in foodstuffs intended for human consumption [1], and in particular Article 3(3)(a) thereof,

After consulting the Scientific Committee on Food (SCF) and the European Food Safety Authority (EFSA),

Whereas:

(1) Commission Directive 2008/84/EC of 27 August 2008 laying down specific purity criteria on food additives other than colours and sweeteners [2] sets out the purity criteria for the additives mentioned in European Parliament and Council Directive 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners [3].

(2) The European Food Safety Authority (hereinafter EFSA) concluded in its opinion of 20 October 2006 [4] that nisin produced through a modified production process using a sugar-based medium is equivalent with respect to health protection to the one produced by the original milk-based medium process. On the basis of that opinion, the existing specifications for E234 nisin should be amended in order to adapt the definition and the purity criteria set out for that additive.

(3) Formaldehyde is used as a preservative during the manufacture of alginic acid, alginate salts and esters of alginic acid. It has been reported that residual formaldehyde, up to 50 mg/kg, may be present in the final gelling additives. At the request of the Commission, EFSA assessed the safety in use of formaldehyde as a preservative during the manufacture and preparation of food additives [5]. EFSA in its opinion of 30 November 2006 concluded that the estimated exposure to gelling additives containing residual formaldehyde at the level of 50 mg/kg of additive would be of no safety concern. Therefore the existing purity criteria for E400 alginic acid, E401 sodium alginate, E402 potassium alginate, E403 ammonium alginate, E404 calcium alginate, and E405 propane-1,2-diol alginate should be amended in such a way that the maximum level of formaldehyde is set at 50 mg/kg.

(4) Formaldehyde is not currently used in the processing of seaweeds for the production of E407 carrageenan and E407a processed eucheuma seaweed. However, it may be naturally occurring in marine algae and be consequently present as an impurity in the finished product. It is therefore appropriate to fix a maximum level of adventitious presence of the above substance in those food additives.

(5) Guar gum is authorised as a food additive for use in foodstuffs by Directive 95/2/EC. In particular, it is used as thickener, emulsifier, and stabiliser. A request to use a partially depolymerised guar gum as a food additive, produced from native guar gum by one of the three manufacturing processes consisting of heat treatment, acid hydrolysis or alkaline oxidation, was submitted to the Commission. EFSA assessed the safety in use of

[1] OJ L 40, 11.2.1989, p. 27.
[2] OJ L 253, 20.9.2008, p. 1.
[3] OJ L 61, 18.3.1995, p. 1.
[4] http://www.efsa.europa.eu/en/science/afc/afc_opinions/ej314b_nisin.html
[5] Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request from the Commission related to use of formaldehyde as a preservative during the manufacture and preparation of food additives; Question No EFSA Q-2005-032. http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178620766610.htm

that additive and, in its opinion of 4 July 2007 [1], estimated that partially depolymerised guar gum has been shown to be very similar to native guar gum with respect to the composition of the final product. It also concluded that partially depolymerised guar gum is of no safety concern for its use as thickener, emulsifier or stabiliser. However, in the same opinion, EFSA recommended that the specifications for E412 guar gum should be adjusted to take into account the increased level of salts and the possible presence of undesirable by-products that may result from the manufacturing process. On the basis of the recommendations issued by EFSA, the specifications of guar gum should be amended.

(6) It is necessary to adopt specifications for E504(i) magnesium carbonate authorised as a food additive for use in foodstuffs through Directive 95/2/EC.

(7) On the basis of data provided by the European Lime Association, it appears that the manufacturing of lime products from available raw materials does not permit them to comply with the existing purity criteria set for E526 calcium hydroxide and E529 calcium oxide, as regards the level of magnesium and alkali salts. Taking into account that magnesium salts are of no safety concern and the specifications as set out in the Codex Alimentarius as drafted by the Joint FAO/WHO Expert Committee on Food Additives (hereafter JECFA), it is appropriate to adjust the levels of magnesium and alkali salts for E526 calcium hydroxide and E529 calcium oxide to the lowest achievable values, which remain lower or equal to the levels set by JECFA.

(8) In addition, it is necessary to take into account the specifications as set out in the Codex Alimentarius drafted by JECFA with regard to the level of lead for E526 calcium hydroxide and E529 calcium oxide. However, due to the natural high background of lead contained in the raw material (calcium carbonate) extracted in some Member States, and from which those additives are derived, it appears difficult to align the level of lead contained in those food additives with the upper limit of lead set by JECFA. Therefore the current level of lead should be reduced to the lowest achievable threshold.

(9) E 901 beeswax is authorised as a food additive in Directive 95/2/EC. EFSA in its opinion of 27 November 2007 [2] confirmed the safety in use of this food additive. However, it also indicated that the presence of lead should be restricted to the lowest possible level. Taking into account the revised specifications for beeswax as set out in the Codex Alimentarius as drafted by JECFA, it is appropriate to amend the existing purity criteria for E901 beeswax in order to lower the maximum permitted level of lead.

(10) Highly refined waxes deriving from synthetic hydrocarbon feedstock (synthetic waxes) and from petroleum based feedstock were jointly evaluated by the Scientific Committee on Food (hereinafter SCF) [3] and an opinion on mineral and synthetic hydrocarbons was issued on 22 September 1995. The SCF considered that sufficient data had been provided to allocate a full group ADI (acceptable daily intake), covering both types of waxes, i.e. waxes deriving from petroleum based or synthetic hydrocarbon feed stocks. When purity criteria for E905 microcrystalline wax were established, the synthetic hydrocarbon waxes were omitted and not included in the specifications. The Commission considers it therefore necessary to amend the purity criteria for E905 microcrystalline wax in order to also cover waxes derived from synthetic hydrocarbon feedstocks.

(11) E230 (biphenyl) and E233 (thiabendazole) are no longer permitted as food additives in the EU legislation. These substances have been removed respectively by Directive 2003/114/EC and Directive 98/72/EC. Consequently, the Annex I to Directive 2008/84/EC should be updated accordingly and the specifications to E230 and E233 should be withdrawn.

(12) It is necessary to take into account the specifications and analytical techniques for additives as set out in the Codex Alimentarius drafted by the JECFA. In particular where appropriate, the specific purity criteria need to be adapted to reflect the limits for individual heavy metals of interest.

(13) Directive 2008/84/EC should therefore be amended accordingly.

(14) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee on the Food Chain and Animal Health,

HAS ADOPTED THIS DIRECTIVE:

Article 1

The Annex I to Directive 2008/84/EC is amended in accordance with the Annex to this Directive.

[1] Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food on a request from the Commission related to an application on the use of partially depolymerised guar gum as a food additive; Question No EFSA-Q-2006-122. http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178638739757.htm

[2] Beeswax (E 901) as a glazing agent and as carrier for flavours; Scientific Opinion of the Panel on food additives, flavourings, processing aids and materials in contact with food (AFC); Question No EFSA-Q-2006-021. http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178672652158.htm

[3] http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_37.pdf

Article 2

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 13 February 2010 at the latest. They shall forthwith communicate to the Commission the text of those provisions.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 3

This Directive shall enter into force on the 20th day following its publication in the *Official Journal of the European Union*.

Article 4

This Directive is addressed to the Member States.

Done at Brussels, 13 February 2009.

For the Commission
Androulla VASSILIOU
Member of the Commission

ANNEX

The Annex I to Directive 2008/84/EC is amended as follows:

1. The text concerning E 234 nisin is replaced by the following:

'**E 234 NISIN**

Definition	Nisin consists of several closely related polypeptides produced during the fermentation of a milk or sugar medium by certain natural strains of *Lactococcus lactis subsp.lactis*
Einecs	215-807-5
Chemical formula	$C_{143}H_{230}N_{42}O_{37}S_7$
Molecular weight	3 354,12
Assay	Nisin concentrate contains not less than 900 units per mg in a mixture of non-fat milk proteins or fermented solids and a minimum sodium chloride content of 50 %
Description	White powder
Purity	
Loss on drying	Not more than 3 % when dried to constant weight at 102 °C to 103 °C
Arsenic	Not more than 1 mg/kg
Lead	Not more than 1 mg/kg
Mercury	Not more than 1 mg/kg'

2. The text concerning E 400 alginic acid is replaced by the following:

'**E 400 ALGINIC ACID**

Definition	Linear glycuronoglycan consisting mainly of β-(1-4) linked D-mannuronic and α-(1-4) linked L-guluronic acid units in pyranose ring form. Hydrophilic colloidal carbohydrate extracted by the use of dilute alkali from natural strains of various species of brown seaweeds (*Phaeophyceae*)
Einecs	232-680-1
Chemical formula	$(C_6H_8O_6)_n$
Molecular weight	10 000-600 000 (typical average)
Assay	Alginic acid yields, on the anhydrous basis, not less than 20 % and not more than 23 % of carbon dioxide (CO_2), equivalent to not less than 91 % and not more than 104,5 % of alginic acid $(C_6H_8O_6)_n$ (calculated on equivalent weight basis of 200)
Description	Alginic acid occurs in filamentous, grainy, granular and powdered forms. It is a white to yellowish brown and nearly odourless

Identification	
A. Solubility	Insoluble in water and organic solvents, slowly soluble in solutions of sodium carbonate, sodium hydroxide and trisodium phosphate
B. Calcium chloride precipitation test	To a 0,5 % solution of the sample in 1 M sodium hydroxide solution, add one fifth of its volume of a 2,5 % solution of calcium chloride. A voluminous, gelatinous precipitate is formed. This test distinguishes alginic acid from acacia gum, sodium carboxymethyl cellulose, carboxymethyl starch, carrageenan, gelatin, gum ghatti, karaya gum, locust bean gum, methyl cellulose and tragacanth gum
C. Ammonium sulphate precipitation test	To a 0,5 % solution of the sample in 1 M sodium hydroxide solution, add one half of its volume of a saturated solution of ammonium sulphate. No precipitate is formed. This test distinguishes alginic acid from agar, sodium carboxymethyl cellulose, carrageenan, de-esterified pectin, gelatin, locust bean gum, methyl cellulose and starch
D. Colour reaction	Dissolve as completely as possible 0,01 g of the sample by shaking with 0,15 ml of 0,1 N sodium hydroxide and add 1 ml of acid ferric sulphate solution. Within 5 minutes, a cherry-red colour develops that finally becomes deep purple
Purity	
pH of a 3 % suspension	Between 2,0 and 3,5
Loss on drying	Not more than 15 % (105 °C, 4 hours)
Sulphated ash	Not more than 8 % on the anhydrous basis
Sodium hydroxide (1 M solution)	Not more than 2 % on the anhydrous basis insoluble matter
Formaldehyde	Not more than 50 mg/kg
Arsenic	Not more than 3 mg/kg
Lead	Not more than 5 mg/kg
Mercury	Not more than 1 mg/kg
Cadmium	Not more than 1 mg/kg
Total plate count	Not more than 5 000 colonies per gram
Yeast and moulds	Not more than 500 colonies per gram
E. coli	Absent in 5 g
Salmonella spp.	Absent in 10 g'

3. The text concerning E 401 sodium alginate is replaced by the following:

'**E 401 SODIUM ALGINATE**

Definition	
Chemical name	Sodium salt of alginic acid
Chemical formula	$(C_6H_7NaO_6)_n$
Molecular weight	10 000-600 000 (typical average)

Assay	Yields, on the anhydrous basis, not less than 18 % and not more than 21 % of carbon dioxide corresponding to not less than 90,8 % and not more than 106,0 % of sodium alginate (calculated on equivalent weight basis of 222)
Description	Nearly odourless, white to yellowish fibrous or granular powder
Identification	
Positive test for sodium and alginic acid	
Purity	
Loss on drying	Not more than 15 % (105 °C, 4 hours)
Water-insoluble matter	Not more than 2 % on the anhydrous basis
Formaldehyde	Not more than 50 mg/kg
Arsenic	Not more than 3 mg/kg
Lead	Not more than 5 mg/kg
Mercury	Not more than 1 mg/kg
Cadmium	Not more than 1 mg/kg
Total plate count	Not more than 5 000 colonies per gram
Yeast and moulds	Not more than 500 colonies per gram
E. coli	Absent in 5 g
Salmonella spp.	Absent in 10 g'

4. The text concerning E 402 potassium alginate is replaced by the following:

'**E 402 POTASSIUM ALGINATE**

Definition	
Chemical name	Potassium salt of alginic acid
Chemical formula	$(C_6H_7KO_6)_n$
Molecular weight	10 000-600 000 (typical average)
Assay	Yields, on the anhydrous basis, not less than 16,5 % and not more than 19,5 % of carbon dioxide corresponding to not less than 89,2 % and not more than 105,5 % of potassium alginate (calculated on an equivalent weight basis of 238)
Description	Nearly odourless, white to yellowish fibrous or granular powder
Identification	
Positive test for potassium and for alginic acid	

Purity	
Loss on drying	Not more than 15 % (105 °C, 4 hours)
Water-insoluble matter	Not more than 2 % on the anhydrous basis
Formaldehyde	Not more than 50 mg/kg
Arsenic	Not more than 3 mg/kg
Lead	Not more than 5 mg/kg
Mercury	Not more than 1 mg/kg
Cadmium	Not more than 1 mg/kg
Total plate count	Not more than 5 000 colonies per gram
Yeast and moulds	Not more than 500 colonies per gram
E. coli	Absent in 5 g
Salmonella spp.	Absent in 10 g'

5. The text concerning E 403 ammonium alginate is replaced by the following:

'**E 403 AMMONIUM ALGINATE**

Definition	
Chemical name	Ammonium salt of alginic acid
Chemical formula	$(C_6H_{11}NO_6)_n$
Molecular weight	10 000-600 000 (typical average)
Assay	Yields, on the anhydrous basis, not less than 18 % and not more than 21 % of carbon dioxide corresponding to not less than 88,7 % and not more than 103,6 % ammonium alginate (calculated on an equivalent weight basis of 217)
Description	White to yellowish fibrous or granular powder
Identification	
Positive test for ammonium and alginic acid	
Purity	
Loss on drying	Not more than 15 % (105 °C, 4 hours)
Sulphated ash	Not more than 7 % on the dried basis
Water-insoluble matter	Not more than 2 % on the anhydrous basis
Formaldehyde	Not more than 50 mg/kg

Arsenic	Not more than 3 mg/kg
Lead	Not more than 5 mg/kg
Mercury	Not more than 1 mg/kg
Cadmium	Not more than 1 mg/kg
Total plate count	Not more than 5 000 colonies per gram
Yeast and moulds	Not more than 500 colonies per gram
E. coli	Absent in 5 g
Salmonella spp.	Absent in 10 g'

6. The text concerning E 404 calcium alginate is replaced by the following:

'**E 404 CALCIUM ALGINATE**

Synonyms	Calcium salt of alginate
Definition	
Chemical name	Calcium salt of alginic acid
Chemical formula	$(C_6H_7Ca_{1/2}O_6)_n$
Molecular weight	10 000-600 000 (typical average)
Assay	Yields, on the anhydrous basis, not less than 18 % and not more than 21 % carbon dioxide corresponding to not less than 89,6 % and not more than 104,5 % of calcium alginate (calculated on an equivalent weight basis of 219)
Description	Nearly odourless, white to yellowish fibrous or granular powder
Identification	
Positive test for calcium and alginic acid	
Purity	
Loss on drying	Not more than 15,0 % (105 °C, 4 hours)
Formaldehyde	Not more than 50 mg/kg
Arsenic	Not more than 3 mg/kg
Lead	Not more than 5 mg/kg
Mercury	Not more than 1 mg/kg
Cadmium	Not more than 1 mg/kg
Total plate count	Not more than 5 000 colonies per gram

Yeast and moulds	Not more than 500 colonies per gram
E. coli	Absent in 5 g
Salmonella spp.	Absent in 10 g'

7. The text concerning E 405 propane-1,2-diol alginate is replaced by the following:

'**E 405 PROPANE-1,2-DIOL ALGINATE**

Synonyms	Hydroxypropyl alginate
	1,2-propanediol ester of alginic acid
	Propylene glycol alginate
Definition	
Chemical name	Propane-1,2-diol ester of alginic acid; varies in composition according to its degree of esterification and the percentage of free and neutralised carboxyl groups in the molecule
Chemical formula	$(C_9H_{14}O_7)_n$ (esterified)
Molecular weight	10 000-600 000 (typical average)
Assay	Yields, on the anhydrous basis, not less than 16 % and not more than 20 % of CO_2 of carbon dioxide
Description	Nearly odourless, white to yellowish brown fibrous or granular powder
Identification	
Positive test for 1,2-propanediol and alginic acid after hydrolysis	
Purity	
Loss on drying	Not more than 20 % (105 °C, 4 hours)
Total propane-1,2-diol content	Not less than 15 % and not more than 45 %
Free propane-1,2-diol content	Not more than 15 %
Water-insoluble matter	Not more than 2 % on the anhydrous basis
Formaldehyde	Not more than 50 mg/kg
Arsenic	Not more than 3 mg/kg
Lead	Not more than 5 mg/kg
Mercury	Not more than 1 mg/kg
Cadmium	Not more than 1 mg/kg
Total plate count	Not more than 5 000 colonies per gram
Yeast and moulds	Not more than 500 colonies per gram

E. coli	Absent in 5 g
Salmonella spp.	Absent in 10 g'

8. The text concerning E 407 carrageenan is replaced by the following:

'**E 407 CARRAGEENAN**

Synonyms	Products of commerce are sold under different names such as: Irish moss gelose Eucheuman (from *Eucheuma* spp.) Iridophycan (from *Iridaea* spp.) Hypnean (from *Hypnea* spp.) Furcellaran or Danish agar (from *Furcellaria fastigiata*) Carrageenan (from *Chondrus* and *Gigartina* spp.)
Definition	Carrageenan is obtained by aqueous extraction of natural strains of seaweeds of *Gigartinaceae, Solieriaceae, Hypneaeceae* and *Furcellariaceae*, families of the class *Rhodophyceae* (red seaweeds). No organic precipitant shall be used other than methanol, ethanol and propane-2-ol. Carrageenan consists chiefly of the potassium, sodium, magnesium and calcium salts of polysaccharide sulphate esters which, on hydrolysis, yield galactose and 3,6-anhydrogalactose. Carrageenan shall not be hydrolysed or otherwise chemically degraded. Formaldehyde may be present as an adventitious impurity up to a maximum level of 5 mg/kg
Einecs	232-524-2
Description	Yellowish to colourless, coarse to fine powder which is practically odourless
Identification	
Positive tests for galactose, for anhydrogalactose and for sulphate	
Purity	
Methanol, ethanol, propane-2-ol content	Not more than 0,1 % singly or in combination
Viscosity of a 1,5 % solution at 75 °C	Not less than 5 mPa.s
Loss on drying	Not more than 12 % (105 °C, four hours)
Sulphate	Not less than 15 % and not more than 40 % on the dried basis (as SO_4)
Ash	Not less than 15 % and not more than 40 % determined on the dried basis at 550 °C

Acid-insoluble ash	Not more than 1 % on the dried basis (insoluble in 10 % hydrochloric acid)
Acid-insoluble matter	Not more than 2 % on the dried basis (insoluble in 1 % v/v sulphuric acid)
Low molecular weight carrageenan (Molecular weight fraction below 50 kDa)	Not more than 5 %
Arsenic	Not more than 3 mg/kg
Lead	Not more than 5 mg/kg
Mercury	Not more than 1 mg/kg
Cadmium	Not more than 2 mg/kg
Total plate count	Not more than 5 000 colonies per gram
Yeast and moulds	Not more than 300 colonies per gram
E. coli	Absent in 5 g
Salmonella spp.	Absent in 10 g'

9. The text concerning E 407a processed eucheuma seaweed is replaced by the following:

'**E 407a PROCESSED EUCHEUMA SEAWEED**

Synonyms	PES (acronym for processed eucheuma seaweed)
Definition	Processed eucheuma seaweed is obtained by aqueous alkaline (KOH) treatment of the natural strains of seaweeds *Eucheuma cottonii* and *Eucheuma spinosum*, of the class *Rhodophyceae* (red seaweeds) to remove impurities and by fresh water washing and drying to obtain the product. Further purification may be achieved by washing with methanol, ethanol or propane-2-ol and drying. The product consist chiefly of the potassium salt of polysaccharide sulphate esters which, on hydrolysis, yield galactose and 3,6-anhydrogalactose. Sodium, calcium and magnesium salts of the polysaccharide sulphate esters are present in lesser amounts. Up to 15 % algal cellulose is also present in the product. The carrageenan in processed eucheuma seaweed shall not be hydrolysed or otherwise chemically degraded. Formaldehyde may be present as an adventitious impurity up to a maximum level of 5 mg/kg.
Description	Tan to yellowish, coarse to fine powder which is practically odourless
Identification	
A. Positive tests for galactose, for anhydrogalactose and for sulphate	
B. Solubility	Forms cloudy viscous suspensions in water. Insoluble in ethanol
Purity	
Methanol, ethanol, propane-2-ol content	Not more than 0,1 % singly or in combination
Viscosity of a 1,5 % solution at 75 °C	Not less than 5 mPa.s

Loss on drying	Not more than 12 % (105 °C, four hours)
Sulphate	Not less than 15 % and not more than 40 % on the dried basis (as SO_4)
Ash	Not less than 15 % and not more than 40 % determined on the dried basis at 550 °C
Acid-insoluble ash	Not more than 1 % on the dried basis (insoluble in 10 % hydrochloric acid)
Acid-insoluble matter	Not less than 8 % and not more than 15 % on the dried basis (insoluble in 1 % v/v sulphuric acid)
Low molecular weight carrageenan (Molecular weight fraction below 50 kDa)	Not more than 5 %
Arsenic	Not more than 3 mg/kg
Lead	Not more than 5 mg/kg
Mercury	Not more than 1 mg/kg
Cadmium	Not more than 2 mg/kg
Total plate count	Not more than 5 000 colonies per gram
Yeast and moulds	Not more than 300 colonies per gram
E. coli	Absent in 5 g
Salmonella spp.	Absent in 10 g'

10. The text concerning E 412 guar gum is replaced by the following:

'**E 412 GUAR GUM**

Synonyms	Gum cyamopsis
	Guar flour
Definition	Guar gum is the ground endosperm of the seeds of natural strains of the guar plant, *Cyamopsis tetragonolobur* (L.) Taub. (family *Leguminosae*). Consists mainly of a high molecular weight hydrocolloidal polysaccharide composed of galactopyranose and mannopyranose units combined through glycosidic linkages, which may be described chemically as a galactomannan. The gum may be partially hydrolysed by either heat treatment, mild acid or alkaline oxidative treatment for viscosity adjustment.
Einecs	232-536-0
Molecular weight	Consists mainly of a high molecular weight hydrocolloidal polysaccharide (50 000-8 000 000)
Assay	Galactomannan content not less than 75 %
Description	A white to yellowish-white, nearly odourless powder
Identification	
A. Positive tests for galactose and for mannose	
B. Solubility	Soluble in cold water

Purity	
Loss on drying	Not more than 15 % (105 °C, 5 hours)
Ash	Not more than 5,5 % determined at 800 °C
Acid-insoluble matter	Not more than 7 %
Protein (N × 6,25)	Not more than 10 %
Starch	Not detectable by the following method: to a 1 in 10 solution of the sample add a few drops of iodine solution (no blue colour is produced)
Organic peroxides	Not more than 0,7 meq active oxygen/kg sample
Furfural	Not more than 1 mg/kg
Lead	Not more than 2 mg/kg
Arsenic	Not more than 3 mg/kg
Mercury	Not more than 1 mg/kg
Cadmium	Not more than 1 mg/kg'

11. After the entry E 503(ii), the following text concerning E 504(i) is added:

'**E 504(i) MAGNESIUM CARBONATE**

Synonyms	Hydromagnesite
Definition	Magnesium carbonate is a basic hydrated or a monohydrated magnesium carbonate or a mixture of the two
Chemical name	Magnesium carbonate
Chemical formula	$MgCO_3.nH_2O$
Einecs	208-915-9
Assay	Not less than 24 % and not more than 26,4 % of Mg
Description	Odourless, light, white friable masses or as a bulky white powder
Identification	
A. Solubility	Practically insoluble both in water or ethanol
B. Positive tests for magnesium and for carbonate	
Purity	
Acid insoluble matter	Not more than 0,05 %
Water soluble matter	Not more than 1 %
Calcium	Not more than 0,4 %

Arsenic	Not more than 4 mg/kg
Lead	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg'

12. The text concerning E 526 calcium hydroxide is replaced by the following:

'**E 526 CALCIUM HYDROXIDE**

Synonyms	Slaked lime, hydrated lime
Definition	
Chemical name	Calcium hydroxide
Einecs	215-137-3
Chemical formula	$Ca(OH)_2$
Molecular weight	74,09
Assay	Content not less than 92 %
Description	White powder
Identification	
A. Positive tests for alkali and for calcium	
B. Solubility	Slightly soluble in water. Insoluble in ethanol. Soluble in glycerol
Purity	
Acid insoluble ash	Not more than 1,0 %
Magnesium and alkali salts	Not more than 2,7 %
Barium	Not more than 300 mg/kg
Fluoride	Not more than 50 mg/kg
Arsenic	Not more than 3 mg/kg
Lead	Not more than 6 mg/kg'

13. The text concerning E 529 calcium oxide is replaced by the following:

'**E 529 CALCIUM OXIDE**

Synonyms	Burnt lime
Definition	
Chemical name	Calcium oxide
Einecs	215-138-9

Chemical formula	CaO
Molecular weight	56,08
Assay	Content not less than 95 % on the ignited basis
Description	Odourless, hard, white or greyish white masses of granules, or white to greyish powder
Identification	
A. Positive test for alkali and for calcium	
B. Heat is generated on moistening the sample in water	
C. Solubility	Slightly soluble in water. Insoluble in ethanol. Soluble in glycerol
Purity	
Loss on ignition	Not more than 10 % (ca. 800 °C to constant weight)
Acid insoluble matter	Not more than 1 %
Barium	Not more than 300 mg/kg
Magnesium and alkali salts	Not more than 3,6 %
Fluoride	Not more than 50 mg/kg
Arsenic	Not more than 3 mg/kg
Lead	Not more than 7 mg/kg'

14. The text concerning E 901 beeswax is replaced by the following:

'**E 901 BEESWAX**

Synonyms	White wax, yellow wax
Definition	Yellow beeswax is the wax obtained by melting the walls of the honeycomb made by the honey bee, *Apis mellifera L.*, with hot water and removing foreign matter
	White beeswax is obtained by bleaching yellow beeswax
Einecs	232-383-7 (beeswax)
Description	Yellowish white (white form) or yellowish to greyish brown (yellow form) pieces or plates with a fine-grained and non-crystalline fracture, having an agreeable, honey-like odour
Identification	
A. Melting range	Between 62 °C and 65 °C
B. Specific gravity	About 0,96
C. Solubility	Insoluble in water
	Sparingly soluble in alcohol
	Very soluble in chloroform and ether

Purity	
Acid value	Not less than 17 and not more than 24
Saponification value	87-104
Peroxide value	Not more than 5
Glycerol and other polyols	Not more than 0,5 % (as glycerol)
Ceresin, paraffins and certain other waxes	Absent
Fats, Japan wax, rosin and soaps	Absent
Arsenic	Not more than 3 mg/kg
Lead	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg'

15. The text concerning E 905 microcrystalline wax is replaced by the following:

'**E 905 MICROCRYSTALLINE WAX**

Synonyms	Petroleum wax, hydrocarbon wax, Fischer-Tropsch wax, synthetic wax, synthetic paraffin
Definition	Refined mixtures of solid, saturated hydrocarbons, obtained from petroleum or synthetic feedstocks
Description	White to amber, odourless wax
Identification	
A. Solubility	Insoluble in water, very slightly soluble in ethanol
B. Refractive Index	n_D^{100} 1,434-1,448
	Alternative: n_D^{120} 1,426-1,440
Purity	
Molecular weight	Average not less than 500
Viscosity	Not less than $1,1 \times 10^{-5}$ m^2 s^{-1} at 100 °C
	Alternative: Not less than $0,8 \times 10^{-5}$ m^2 s^{-1} at 120 °C, if solid at 100 °C
Residue on ignition	Not more than 0,1 wt %
Carbon number at 5 % distillation point	Not more than 5 % of molecules with carbon number less than 25
Colour	Passes test
Sulphur	Not more than 0,4 wt %
Arsenic	Not more than 3 mg/kg

Lead	Not more than 3 mg/kg
Polycyclic aromatic compounds	The polycyclic aromatic hydrocarbons, obtained by extraction with dimethyl sulfoxide, shall meet the following ultraviolet absorbency limits:

Nm	Maximum absorbance per cm path length
280-289	0,15
290-299	0,12
300-359	0,08
360-400	0,02

Alternative, if solid at 100 °C

PAC method as per 21 CFR& 175.250;

Absorbency at 290 nm in decahydronaphthalene at 88 °C: Not exceeding 0,01'

16. The text concerning E 230 and E 233 is deleted.

II

(Acts adopted under the EC Treaty/Euratom Treaty whose publication is not obligatory)

DECISIONS

COMMISSION

COMMISSION DECISION

of 13 February 2009

on the Community's financial contribution to a programme for the control of organisms harmful to plants and plant products in the French overseas departments for 2009

(notified under document number C(2009) 801)

(Only the French text is authentic)

(2009/126/EC)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Regulation (EC) No 247/2006 of 30 January 2006 laying down specific measures for agriculture in the outermost regions of the Union [1], and in particular the first sentence of the first subparagraph of Article 17(3),

Whereas:

(1) Growing conditions in the French overseas departments require special measures concerning crop production. Those measures include expensive plant health measures.

(2) Commission Decision 2007/609/EC of 10 September 2007 on the definition of the measures eligible for Community financing in the programmes for the control of organisms harmful to plants and plant products in the French overseas departments, in the Azores and in Madeira [2] defines the measures eligible for Community financing under programmes for the control of organisms harmful to plants and plant products in the French overseas departments, the Azores and Madeira.

(3) The French authorities have submitted to the Commission a programme for 2009 providing for plant health measures in the French overseas departments. That programme specifies the objectives to be achieved, the expected deliverables, the measures to be carried out, their duration and their cost with a view to a possible Community financial contribution. The measures provided for in that programme fulfill the requirements of Decision 2007/609/EC.

(4) In accordance with Article 3(2)(a) of Council Regulation (EC) No 1290/2005 of 21 June 2005 on the financing of the common agricultural policy [3], plant-health measures are to be financed from the European Agricultural Guarantee Fund. For the purposes of financial control of those measures Articles 9, 36 and 37 of that Regulation apply.

(5) The measures provided for in this Decision are in accordance with the opinion of the Standing Committee on Plant Health,

HAS ADOPTED THIS DECISION:

Article 1

A Community financial contribution to France for the official programme for the control of organisms harmful to plants and plant products in the French overseas departments for 2009 as specified in Part A of the Annex, is approved.

[1] OJ L 42, 14.2.2006, p. 1.
[2] OJ L 242, 15.9.2007, p. 20.
[3] OJ L 209, 11.8.2005, p. 1.

It shall be limited to 60 % of the total eligible expenditure, as specified in Part B of the Annex, with a maximum of EUR 246 660 (VAT excluded).

Article 2

1. An advance of EUR 100 000 shall be paid within 60 days after receipt of a request for payment by France.

2. The balance of the financial contribution shall be paid provided that a final implementation report on the programme is submitted to the Commission in electronic form by 15 March 2010 at the latest.

That report shall contain:

(a) a concise technical evaluation of the entire programme, including the degree of achievement of physical and qualitative objectives and the progress accomplished, and an assessment of the immediate phytosanitary and economic impact; and

(b) a financial cost statement indicating the actual expenditure broken down by sub-programme and by measure.

3. With respect to the indicative budget breakdown specified in Part B of the Annex, France may adjust the financing between different measures in the same sub-programme within a limit of 15 % of the Community contribution to this sub-programme, provided that the total amount of eligible costs scheduled in the programme is not exceeded and that the main objectives of the programme are not thereby compromised.

It shall inform the Commission of any adjustments made.

Article 3

This Decision shall apply from 1 January 2009.

Article 4

This Decision is addressed to the French Republic.

Done at Brussels, 13 February 2009.

For the Commission

Androulla VASSILIOU

Member of the Commission

ANNEX

PROGRAMME AND INDICATIVE BUDGET BREAKDOWN FOR 2009

Part A

PROGRAMME

The programme shall consist of four sub-programmes:

1. inter-departmental sub-programme:
   (a) Measure 1.1: development of detection methods for harmful organisms based on quantitative polymerase chain reaction (PCR);
   (b) Measure 1.2: support to the transfer of Citrus plant material;
2. sub-programme for the department of Martinique:
   (a) Measure 2.1: phytosanitary surveys and set-up of tools for the integrated management of plant health issues;
3. sub-programme for the department of Guyane:
   (a) Measure 3.1: management of an agricultural phytosanitary warning system for rice production;
4. sub-programme for the department of Guadeloupe:
   (a) Measure 4.1: management of a survey network for fruit flies;
   (b) Measure 4.2: management of the risk of introduction of harmful organisms by tourist activity.

Part B

INDICATIVE BUDGET BREAKDOWN

(in EUR, with indication of the various expected deliverables)

Sub-programmes	Deliverables (S: provision of services, R: research or study work)	Eligible expenditure	National contribution	EC contribution
Inter-DOM sub-programme				
Measure 1.1	Method of quantitative PCR (R)	120 000	48 000	72 000
Measure 1.2	Research on *Citrus* plant material (R)	50 000	20 000	30 000
Sub-total		170 000	68 000	102 000
Martinique				
Measure 2.1	Phytosanitary surveys and new control methods for harmful organisms (S)	95 600	38 240	57 360
Sub-total		95 600	38 240	57 360
Guyane				
Measure 3.1	Management of an agricultural phytosanitary warning system (S)	112 000	44 800	67 200
Sub-total		112 000	44 800	67 200
Guadeloupe				
Measure 4.1	Management of a survey network for fruit flies (S)	18 500	7 400	11 100
Measure 4.2	Actions of communication to the public on the risks of introduction of harmful organisms (S)	15 000	6 000	9 000
Sub-total		33 500	13 400	20 100
Total		411 100	164 440	246 660

NOTE TO THE READER

The institutions have decided no longer to quote in their texts the last amendment to cited acts.

Unless otherwise indicated, references to acts in the texts published here are to the version of those acts currently in force.