



EUROPEAN COMMISSION  
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Health systems and products  
**Medicinal products – quality, safety and efficacy**

The rules governing medicinal products  
in the European Union

Volume 6B

# Notice to applicants

Veterinary medicinal products

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Presentation and content of the  
dossier

2015



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## FOREWORD

The Chapters of the Notice to Applicants (NTA) are prepared in consultation with the Competent Authorities of the Member States and the European Medicines Agency. This Notice has no legal force and does not necessarily represent the final views of the Commission. In case of doubt, reference should therefore be made to the appropriate Community Directives. It is important when reading this text to appreciate that the legal requirements of the Directives and the Regulation must be met and that this Notice represents the harmonised views of the Member States on how those requirements may be met.

Volume 6A of the Rules Governing Medicinal Products in the European Union concerns the procedures for marketing authorisation of veterinary medicinal products. Volume 6C contains regulatory guidelines.

### **Volume 6B describes the presentation and content of the application dossier.**

The application dossier, which should be submitted in either a national or Community procedure (i.e. to the Competent Authorities of the Member States or to the European Medicines Agency), consists of administrative information and the necessary demonstration of quality, safety and efficacy of the veterinary medicinal product. The requirements for the content of the application dossier are set out in Annex I of Directive 2001/82/EC, i.e. the particulars and documents accompanying an application for marketing authorisation pursuant to Article 12 of Directive 2001/82/EC.

This update to **Volume 6B** of the Notice to Applicants (NTA) has been necessitated by the revision to Annex I of Directive 2001/82/EC<sup>1</sup>. The revised Annex I entered into force on 6 September 2009.

This volume provides guidance for the compilation of dossiers for applications for marketing authorisation, and is applicable for the centralised procedure and national procedures, including mutual recognition and decentralised procedures.

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<sup>1</sup> 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 (OJ, 12.2.2009, p.10-61)

## INTRODUCTION AND GENERAL PRINCIPLES

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 (the Agency) and the other pharmaceutical Community guidelines published by the Commission in different volumes of *The rules governing medicinal products in the European Union*.

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.

The manufacturing process shall comply with the requirements of Commission Directive 91/412/EEC 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.

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.

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.

Member States shall ensure that all experiments on animals are conducted in accordance with Directive 2010/63/EU<sup>2</sup>.

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 the marketing authorisation has been granted, any change to the content of the dossier shall be submitted to the competent authorities in accordance with Commission Regulation (EC) No 1234/2008 on variations<sup>3</sup>.

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 shall be provided in the dossier. The information shall be presented in

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<sup>2</sup> Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (OJ L 276, 20.10.2010, p. 33).

<sup>3</sup> Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L334, 12.12.2008, p.7)

accordance with the provisions of Directive 2001/18/EC and Regulation (EC) No 726/2004 of the European Parliament and of the Council, taking into account guidance documents published by the Commission.

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.

An electronic version (according to the TIGesVet guideline) can be accepted.

### **Administrative documentation**

**Part 1** is divided into 3 sub-sections. Parts 1A, 1B and 1C are always required. Part 1B must be in the language(s) of the Member State(s) concerned (in English at time of submission for centralised applications). Parts 1 A and 1 C should be submitted in the language of the Member State concerned if so requested in Chapter 7 of Volume 6A of The Notice to Applicants.

- Part 1 A consists of the administrative data, packaging, samples or mock-ups, manufacturing and marketing authorisations applied for or obtained elsewhere (see Application form)
- Part 1 B consists of the proposed Summary of Product Characteristics (SPC), labelling and package leaflet in accordance with Articles 14, 58(1) to (3) and 61 of Directive 2001/82/EC.
  - Part 1 B1 Summary of Product Characteristics (SPC)
  - Part 1 B2 Proposals for Packaging, Labelling & Package Leaflet
  - Part 1 B3 SPCs already approved in the Member States
- Part 1 C consists of the Detailed and Critical Summaries and their tabular formats. There should be separate Detailed and Critical Summaries on the chemical/pharmaceutical/biological, safety/residues and pre-clinical/clinical documentation. With regard to safety/residues, it is preferable for the pharmacology/toxicology, user safety and residues aspects as well as the environmental risk assessment of the Detailed and Critical Summaries to be presented separately. Target animal safety should be presented separately within the pre-clinical/clinical Detailed and Critical Summaries.

### **Technical documentation**

Parts 2, 3 and 4 of the application dossier consist of the chemical, pharmaceutical and biological documentation, the safety and residues documentation, and the pre-clinical and clinical documentation respectively.

A written summary for the relevant sections of Part 3 and Part 4 may facilitate mutual recognition by concerned Member States, and may also assist in the consideration of an application by the members of the Committee for Veterinary Medicinal Products of the European Agency for the Evaluation of Medicinal Products.

Each volume of the dossier should be sequentially paginated throughout, legible and suitably bound.

Full copies of all bibliographical references should be provided.





**VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICAL  
VETERINARY MEDICINAL PRODUCTS**

## **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 or mock-ups, 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 the Article 14 as approved by Member States and a list of countries in which an application has been submitted or refused.

The [application form](#) to be used is available for downloading from the Commission's website.

#### **B. SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET**

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

A proposed labelling text for the immediate and outer packaging shall be provided in accordance with Title V of Directive, together with a package leaflet where one is required pursuant to Article 61.

In addition the applicant shall provide one or more 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**

### **GENERAL**

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 summarized in an appendix, whenever possible in tabular or graphic form (see standard formats provided). 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 to the applicant shall be declared.

It is important to emphasize that well prepared Detailed and Critical Summaries greatly facilitate the task of the competent authority in evaluating the dossier and contribute towards the speedy processing of applications. For these reasons particular care should be taken in the preparation of Detailed and Critical Summaries, which should be written in accordance with the guidance on the preparation of Detailed and Critical Summaries given below.

Authors of Detailed and Critical Summaries must be chosen on the basis of their relevant qualifications and their recognised expertise in the field concerned. Authors should preferably not have been personally involved in the conduct of the tests included in the dossier.

Each Detailed and Critical Summary should consist of:

- an abbreviated product profile
- a critical evaluation of the dossier
- the opinion of the author as to whether sufficient guarantees have been provided as to the suitability of the product for its proposed use
- a summary of all the important data
- the signature of the author and the place and date of the report's issue
- the author's curriculum vitae and a declaration of the author's professional relationship to the applicant
- justification for the statements in the proposed Summary of Product Characteristics taking into account the submitted data.

The product profile should include the following key points:

- a) type of application as detailed in point 3 of the application form.
- b) chemical and pharmacokinetic properties
  - the chemical structure of the active substance(s)
  - the physico-chemical properties of the active substance(s) and the characteristics of the pharmaceutical form which could have an impact on the pharmacokinetic parameters and clinical efficacy
- c) indications
  - the therapeutic indications proposed relevant to the posology and their justification (if necessary for each target species)
  - the pharmacological and therapeutic classification of the active substance(s), defining the mode of action
- d) precautions
  - significant precautions and warnings derived from the principal results of the toxicology and pharmacology studies
- e) marketing authorisations/pharmacovigilance
  - a list of marketing authorisations already issued in other countries, and those applied for
  - a list of any measures resulting from pharmacovigilance

It is essential to note that the Detailed and Critical Summaries must include a critical discussion of the properties of the product as demonstrated by the contents of the dossier.

The author is expected to take and defend a clear position on the final product, in the light of current scientific knowledge. A simple factual summary of the information contained in the application is not sufficient and the Detailed and Critical Summaries must not be a repetition of other parts of the dossier, although important data will need to be summarized in the Detailed and Critical Summaries in some form.

More detailed guidance on the preferred form for summary data in Detailed and Critical Summaries is provided below under the headings of “Quality”, “Safety” and “Efficacy”.

Both Detailed and Critical Summaries and summarized tables must contain precise references to the information contained in the main documentation. If authors wish to supplement their report by reference to additional literature, they must indicate clearly that the applicant has not included this information in the relevant part of the dossier.

Where relevant Community guidelines on the conduct of tests, studies and trials on a medicinal product exist, these should be taken into consideration when Detailed and Critical Summaries are prepared. Any deviation from guidelines should be discussed and justified. In particular, the authors should give a justification for the statements in the proposed SPC, taking into account the submitted data and the current SPC guideline.

For applications submitted through the mutual recognition procedure the Detailed and Critical Summaries and summary tables must cover all the data submitted in support of the application, including any data collected after the submission of the initial application.

For changes to a marketing authorisation leading to an extension application, applications in accordance with Commission Regulation (EC) No 1234/2008 on variations, an application for a new marketing authorisation must be made.

The Detailed and Critical Summaries in this case should particularly focus on the following elements:

- an evaluation of the results of the additional studies. The results should be discussed in the perspective of what is known from published literature and previous submissions. Additional studies should also be submitted in tabular formats provided in this Notice to Applicants;
- an update of published literature relevant to the active substance and the present application. The author may annotate articles published in “peer review” journals, which may be acceptable for this purpose;
- every claim in the SPC not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the Detailed and Critical Summaries and substantiated by published literature and/or additional studies.

Experience has shown that many applications, particularly for new active substances, have included a written summary as well as the tabulations to the Detailed and Critical Summaries.

Competent authorities have generally found these to be helpful. However, it is considered important to clarify the purpose of the appendices to the Detailed and Critical Summaries in order to avoid duplication and overlap.

It is important to avoid duplication, repetition between the Detailed and Critical Summaries and the written summary. Equally, experience has shown that a good tabular presentation with a short written summary is an effective method of communication. Therefore, where tabular formats suffice, it is not necessary to duplicate the message in writing.

For the quality part of the dossier, the tabular formats (Q1 to Q23) are considered to fulfil the function of a written summary (except in the case of medicinal products derived from biotechnology including those, which contain or consist of genetically modified organisms where a written summary of not more than 30 pages would be helpful, see further guidance below).

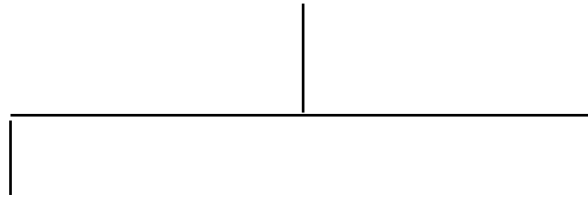
The assessment reports which are prepared by the competent authority in the Member State will also make use of these formats, by the use of annotations.



# DETAILED AND CRITICAL SUMMARIES ON THE PHYSICO-CHEMICAL, BIOLOGICAL AND MICROBIOLOGICAL DOCUMENTATION

## GENERAL ASPECTS

CRITICAL ASSESSMENT OF PART II (Max 10 pages)



TABULAR FORMATS

OPTION TO USE ALTERNATIVE  
TABULATIONS

WRITTEN SUMMARY \*

(Max 30 pages)

OBLIGATORY

RECOMMENDED

- \* For the Quality part of the dossier, the tabular formats are considered to fulfil the function of a written summary (except in case of biotechnology medicinal products and medicinal product which contain or consist of genetically modified organisms where a written summary would be helpful, see further guidance below).

The pharmaceutical Detailed and Critical Summaries should consist of a critical evaluation of the methodology, results and conclusions.

Report formats which may be used by the pharmaceutical author of the critical summary for compiling the factual tabular data are given in succeeding pages.

Use of these tabular formats facilitates a clear and well-ordered tabular presentation of the data. The format can however be adapted as necessary for an individual marketing authorisation application by expanding or contracting sections, adding sections, and omitting sections where not relevant. Alternative tabular presentations may be used, however, the heading of such tables should be of the same structure.

Page references should be included within the formats and should be made to the appropriate volume and page of the Part II documentation or other relevant Parts of the full dossier. The “comments” space within the tabular formats is intended for use by the assessor in the competent authority of the Member State concerned, and should therefore be left blank by the applicant.

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 the Council 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.

When 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 (e.g. for an Active Substance Master File) 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.

It is the responsibility of the applicant for a marketing authorisation for a medicinal product to ensure that complete information is supplied to the authorities. The applicant must therefore consult and work together with the person submitting a separate Active Substance Master File to ensure that all relevant information required is supplied as part of the Chemical, Pharmaceutical and Biological Documentation and in the Pharmaceutical Critical Summary on that documentation.

Confidential data on the manufacture of the active substance(s) may be submitted in separate confidential documentation (Active Substance Master File). However where it is supplied separately, a separate Critical Summary must be provided on any aspects not covered in the application for the marketing authorisation for the product.

## CRITICAL ASSESSMENT

It is assumed, since the pharmaceutical expert has written and signed his Critical Summary, that he is fully convinced that the product as developed, is of the appropriate quality and that the proposed control tests and limits are those appropriate to ensure that the routinely manufactured batches continue to meet this quality requirement. The pharmaceutical expert should therefore not state this as his conclusion but instead critically review and discuss the elements of the dossier and tabular format which led him to this view.

Some elements which might be included in the relevant sections are:

### Composition of the product

A discussion of the differences between the clinical trial formula(e) and the finally chosen composition and the significance of such differences (particularly in relation to product bioavailability).

### Development pharmaceuticals

A discussion of the choice of dosage form in relation to the intended indications. In relation to products where the bioavailability is critical, the data on bioavailability and the proposed routine control tests to ensure batch to batch consistency of bioavailability should be discussed (with a justification for the *in vitro* test limits). Where the *in vivo* absorption of the active substance(s) in the target species is low, the expert should discuss the evidence and conclude whether this relates to the intrinsic properties of the drug or is related to the particular dosage form.

The choice and concentration of additives (preservatives, antioxidants and others) should be discussed and shown to be optimised for their intended purpose in the product. In particular the results of preservative efficacy testing in relation to product storage, reconstitution, dilution and use should be discussed.

## Stereoisomerism

When a new active substance(s) contains one or more chiral centres, it must be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the animal studies, and information given as to the form of the active substance(s) to be used in the final product intended for marketing. Details should be provided on the chemical separation of different chiral forms used in the various tests reported in the application for marketing authorisation.

Possible problems relating to Stereoisomerism, which should be discussed in the appropriate Critical Summary and cross referenced, should include:

The batch to batch consistency of the ratio of stereoisomers in the various batches used;

The toxicological issues (for example those arising from the relative toxicity of the isomers);

The pharmacological aspects (including evidence on *which* stereoisomers have *the* desired pharmacological properties);

Pharmacokinetics (including information on the relative metabolism of the stereoisomers) extrapolation of the preclinical data (paying particular attention to possible problems relating to species differences in handling of the stereoisomers);

The significant clinical issues.

Possible changes in stereochemical purity during manufacture and storage of the active substance and the product.

Where a mixture of stereoisomers has previously been marketed, and it is now proposed to market a product containing only one isomer, full data on this isomer should be provided.

## Method of preparation

A discussion as to how the particular manufacturing method and in-process control tests will consistently guarantee batches of product of the desired quality and that all individual dosage units within the batch are also acceptable.

## Process validation

A discussion as to how the data gives the required assurance of suitable product quality (e.g. that a non-standard sterilisation condition provides an acceptable level of assurance of product sterility).

## Control of pharmacopoeial active substance(s)

A discussion of the impurities in the starting material (particularly if it has been prepared by a method liable to leave impurities not mentioned in the pharmacopoeial monograph). Also in relation to possible impurities which might not be controlled by the pharmacopoeial monograph a cross-reference to the discussion of the possible toxicity of these impurities in the Toxicological Critical Summary, levels found in typical batches, and the proposed test limits.

## Control of non-pharmacopoeial active substance(s)

A discussion on the suitability of the manufacturing method and its controls to routinely and consistently produce material of suitable *quality*, an interpretation of the evidence of structure, isomerism and comment on the physico-chemical characteristics in relation to the specification (e.g. need for a particle size test in relation to a sparingly soluble active substance).

The expert should carefully review data on actual and potential impurities arising from the synthesis and together with the data from the analytical validation studies, show how the control limits on individual and total impurities are set. The expert should also discuss the comparative analysis of the impurity levels in batches of the drug substances used in the toxicology studies, clinical trials and in typical batches as to be used in the marketed product



to see whether the impurity levels have changed, and how the specified impurity limits relate to the levels found.

For active substance(s) (both pharmacopoeial and non-pharmacopoeial), the relevant impurities present in the active substance(s) from the specified manufacturing source must be known to the applicant for a product marketing authorisation, and the toxicopharmacological Critical Summary in the application should, where necessary, consider the relevant impurities present in the active substance(s) and give a critical evaluation of what is known of their potential pharmacological and toxicological effects. The expert will need to consider the proposed impurity limits in relation to the toxicology of the impurity and the active substance(s) itself, the route of administration, daily dose, target animal species and categories, the duration of therapy and the proposed indications for the medicinal product

For vegetable active substances, the test for potential contaminants (micro-organisms, pesticides, fumigants, radioactivity, toxic metals etc.) should be summarized. In the case of vegetable active substances the possibility of accumulation of pesticides or diminution of micro-organisms in comparison with the vegetable active substance and potential residues of fumigants should be discussed with the levels found in typical batches and proposed test limits.

#### Excipients

A discussion of the suitability of the specification proposed. For new excipient(s) full data are needed and there should be a cross-reference to the data in the Toxicology Critical Summary.

#### Packaging material (immediate packaging)

A discussion of the results of the studies on suitability of the packaging material in relation to proposed storage conditions and use of the product (e.g. moisture protection). Also a discussion of the specification and batch results.

#### Control tests on intermediate products

Where some tests on the finished product are not proposed to be carried out routinely because intermediate products are controlled, this should be discussed and justified.

#### Control tests on the finished product

A discussion of the suitability of the proposed specification and control methods. The tests and limits (particularly for the quantitative determination of active substance(s) and purity tests) should be justified in relation to the results of the analytical validation studies, the batch analyses, and any information on production variability (incl. results of process validation studies). The results of production batch analyses should be compared to demonstrate reproducibility of the manufacturing process for the product. If necessary this may need to be provided on an ongoing basis.

#### Stability of the active substance(s)

A discussion of the conclusions as to the variability of batches of drug substance in stability, the most appropriate storage conditions, and the duration of storage before retesting to check compliance with specification. The expert should also discuss the significance of the degradation products and cross-refer to the information on their toxicity in the toxicopharmacological Critical Summary.

#### Stability of the finished product

A discussion of the results of the stability trials and analysis of the data (including information on the active substance(s), content of the active substance(s) and content of significant degradation products, with comment on any discrepancies between these data), and a discussion of the variability between batches of the dosage form in the final packaging.

The method of calculation or estimation of the shelf-life should be explained together with a justification for the recommended storage conditions. The basis for the recommendations on storage during marketing and use should be given.

#### Other information

A discussion of the results of other tests included in Part II, particularly on the validation of metabolic and pharmacokinetic assay methods with regard to the suitability of these methods, should be included.

#### Reference list

A list of references used, in addition to those contained in the dossier, should be given and stated in accordance with internationally accepted standards of the 1979 Vancouver Declaration on "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" or the system used in "Chemical Abstracts".

#### Information on the qualifications and experience of the pharmaceutical expert

The qualifications and experience of the expert should be briefly summarized including the professional relationship with the applicant. Although only one expert may assume responsibility for the report other experts may contribute to it.

## PHARMACEUTICAL QUALITY TABULAR FORMATS

## TABULAR FORMATS FOR THE PHARMACEUTICAL CRITICAL SUMMARY

Notes for guidance on completion of the tabular formats are situated facing the first format to which they refer

2 A	Composition	Format Q1
	Dosage form	
	Development pharmaceuticals	Format Q2
	Development pharmaceuticals	Format Q3
2 B	Description of the manufacturing method	Format Q4
	Process validation	Format Q5
2 C	Control of starting materials	
	Active substance(s) specification and routine tests	Format Q6
	Nomenclature and description	Format Q7
	Non Pharmacopoeial Active substances	
	Active substance manufacture	Format Q8
	Quality control	
	during manufacture	Format Q9
	Development Chemistry	Format Q10
	Analytical development	
	& validation	Format Q11
	Impurities	Format Q12
	Batch analyses	Format Q13
	Excipients	
	Specification and routine tests	Format Q14
	Scientific data	Format Q15
	Packaging material	
	Immediate packaging	Format Q16
2 D	Control tests on intermediate products	Format Q17
2 E	Control tests on the finished product	Format Q18
	Scientific data	Format Q19
2 F	Stability	
	Stability tests on	
	Active substances	Format Q20
	The finished product	Format Q21
	In use stability	Format Q22
2 G	Other information	Format Q23

## PART 2 A – COMPOSITION

The complete qualitative and quantitative composition of the finished product should be given as a unit and/or percentage formula. For active substance(s) consisting of plant material or preparations, it may be necessary to include the amount of all components, which may affect therapeutic activity. A brief description of the container (and closure), the nature of the container materials, and the method of opening should be provided. If the composition of product(s) used in clinical trials differed from the finally chosen composition the differences should be indicated.

Pharmaceutical Critical Summary

Format Q1 - Composition

<p>Name of Company:</p> <p>Name of Finished Medicinal Product:</p> <p>Name of Active substance(s)</p>	<p>Tabular format referring to Part 2 A of the Dossier</p>	<p>(For National Authority Use Only)</p>
<p>PART 2 A: COMPOSITION</p>		
<p>Product Description:                      Volume      Page(s)</p>	<p>(For National Authority Use Only) COMMENTS</p>	
<p>Complete Composition:                      Volume      Page(s)</p>		
<p>Active substance(s) Unit and/or Percentage Formula</p> <p>Excipients</p>		
<p>Container (brief description): Volume      Page(s)</p>		
<p>Clinical trial formulae: Volume      Page(s)</p>		
<p>Active substance(s) Unit and/or Percentage Formula</p> <p>Excipients</p>		

## PART 2 A – DEVELOPMENT PHARMACEUTICS

The essential elements of the pharmaceutical development work carried out to establish that the type of dosage form selected and the formulation proposed are satisfactory for the purposes specified in the application, should be summarized. This summary should explain the choice of composition and how the concentrations of the additives in the formulation was shown to be optimal. A summary of data on compatibility with other products (e.g. for products to be diluted and administered intravenously), and with the container (e.g. sorption, leaching) should also be provided.

A summary of the relevant *in vivo* bioavailability studies and a discussion of the proposed routine control tests to be carried out on batches of the finished product (and which ensure consistent batch to batch control of product: bioavailability) should be provided in this section.

Pharmaceutical Critical Summary

Format Q2 – Dosage form – Development pharmaceuticals

<p>Name of Company:</p> <p>Name of Finished Medicinal Product:</p> <p>Name of Active substance(s)</p>	<p>Tabular format referring to Part 2 A of the Dossier</p>	<p>(For National Authority Use Only)</p>
<p><b>PART 2 A: DOSAGE FORM – DEVELOPMENT PHARMACEUTICS</b></p>		
<p>Product Development Studies Summary:</p> <p>Volume                  Page(s)</p>		<p>(For National Authority Use Only) COMMENTS</p>
<p>Explanation of choice of the composition</p>		
<p>Explanation of optimisation of concentrations of the additives in the composition:</p>		
<p>Summary of studies on compatibility data with other products (if necessary): Volume                  Page(s)</p>		



Pharmaceutical Critical Summary

Format Q3 – Dosage form - Development pharmaceuticals

Name of Company:  Name of Finished Medicinal Product:  Name of Active substance(s)	Tabular format referring to Part 2 A of the Dossier	(For National Authority Use Only)
<b>PART 2 A: DOSAGE FORM – DEVELOPMENT PHARMACEUTICS</b>		
Summary of studies on compatibility with the container/closure: Volume                      Page(s)		(For National Authority Use Only) <b>COMMENTS</b>
Summary of <i>in vivo</i> bioavailability/bioequivalence studies: Volume                      Page(s)		
<i>In vitro</i> dissolution data on products used in the <i>in vivo</i> bioavailability studies: Volume                      Page(s)		

## PART 2 B – DESCRIPTION OF THE MANUFACTURING METHOD

The manufacturing formula, the method of preparation of the finished product, the in-process controls and the particular manufacturing precautions should be summarized.

If vegetable medicinal product preparations are used as starting materials, the description of their manufacturing should be summarized under Part II C format.

Pharmaceutical Critical Summary  
 Format Q4 – Method of preparation

Name of Company:  Name of Finished Medicinal Product:  Name of Active substance(s)	Tabular format referring to Part 2 B of the Dossier	(For National Authority Use Only)	
<b>PART 2 B: METHOD OF PREPARATION</b>			
Manufacturing formula:	Volume	Page(s)	(For National Authority Use Only) <b>COMMENTS</b>
Batch size: Formula:			
Manufacturing process (including in process control and assembly)			

**PART 2 B – PROCESS VALIDATION STUDIES**

The essential elements of the experimental validation work carried out to guarantee that the purposed manufacturing process is a suitable one and consistently yields a product of the desired quality, should be summarized.

Pharmaceutical Critical Summary

Format Q5 – Method of preparation - Process validation

<p>Name of Company:</p> <p>Name of Finished Medicinal Product:</p> <p>Name of Active substance(s)</p>	<p>Tabular format referring to Part 2 B of the Dossier</p>	<p>(For National Authority Use Only)</p>
<p><b>PART 2 B: METHOD OF PREPARATION – PROCESS VALIDATION</b></p>		
<p>Summary of experimental studies:    Volume    Page(s)</p>	<p>(For National Authority Use Only) COMMENTS</p>	
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## PART 2 C – CONTROL OF STARTING MATERIALS

### a) Active substances

For active substance(s) described in a pharmacopoeia, the proposed routine batch tests should be summarized. If these are different to those described in the pharmacopoeia, a summary of the proof that the active substance meets the quality requirements of the pharmacopoeia must be provided.

For a purchased active substance described in a pharmacopoeia, the work carried out to confirm the suitability of the active substance(s) should be summarized. If the method of manufacture of the active substance(s) gives reason to expect impurities which are not accounted for by the pharmacopoeial monograph, then information on the routine additional tests and batch analysis to support their use and their proposed limits should be provided.

If the starting material is of vegetable origin, the monograph of the material should be summarized (specification with description of the test procedures). Only the substances of vegetable origin that determine the therapeutic activity of the product should be stated.

For active substances of vegetable origin and preparations, the test for the potential contaminant (micro-organisms, pesticides, fumigants, toxic metals, radioactivity etc.) should be summarized.

For active substance(s) not described in a pharmacopoeia (including new active substances) the specification and routine tests, the scientific data on nomenclature, description, manufacture, quality control during manufacture, the development chemistry (including evidence of structure, potential isomerism, physico-chemical characteristics and analytical validation,) potential and actual impurities and the batch analysis should be summarized.

Pharmaceutical Critical Summary

Format Q6 – Control of starting materials - Active substance(s): Specification and active tests

Name of Company:  Name of Finished Medicinal Product:  Name of Active substance(s)	Tabular format referring to Part 2 C of the Dossier	(For National Authority Use Only)
<b>PART 2 C: CONTROL OF STARTING MATERIALS – ACTIVE SUBSTANCE(S): Specifications and active tests</b>		
Specifications and routine tests: Volume                                  Page(s)	(For National Authority Use Only) COMMENTS	
(a) Active substance(s) described in a pharmacopoeia  (b) Active substance(s) not described in a pharmacopoeia		
Summary of specifications and Routine Tests – Characteristics: Volume                                  Page(s)		
Identification tests:                  Page(s)		
Purity tests:                                  Page(s)		
Physical:  Chemical:  Biological/Immunological:		
Other tests:                                  Page(s)		
Assay/Other evaluation of potency:          Page(s)		

Pharmaceutical Critical Summary

Format Q7 – Control of starting materials - Active substance(s): Nomenclature and description

<p>Name of Company:</p> <p>Name of Finished Medicinal Product:</p> <p>Name of Active substance(s)</p>	<p>Tabular format referring to Part 2 C of the Dossier</p>	<p>(For National Authority Use Only)</p>
<p><b>PART 2 C: CONTROL OF STARTING MATERIALS – ACTIVE SUBSTANCE(S):</b> Nomenclature and description</p>		
<p>Structural Relationship to Other Known Drugs</p>		<p>(For National Authority Use Only) COMMENTS</p>
<p>1. Nomenclature:      Volume      Page(s)</p>		
<p>INN:</p> <p>Chemical name:</p> <p>Other name:</p> <p>Laboratory code:</p> <p>National approved name:</p> <p>For starting materials of vegetable origin:</p> <p>Botanical name and authority:</p> <p>Definition of preparation of vegetable origin:</p>		
<p>2. Description:      Volume      Page(s)</p>		
<p>Physical form:</p>		
<p>Structural formula (include conformation if necessary):</p>		
<p>Molecular formula:</p>	<p>Relative Molecular mass:</p>	
<p>Chirality:</p>		

Pharmaceutical Critical Summary

Format Q8 – Control of starting materials - Active substance(s): Manufacture

Name of Company:  Name of Finished Medicinal Product:  Name of Active substance(s)	Tabular format referring to Part 2 C of the Dossier	(For National Authority Use Only)
<b>PART 2 C: CONTROL OF STARTING MATERIALS – ACTIVE SUBSTANCE(S): Manufacture</b>		
Name and address of manufacturing sources:  Volume                      Page(s)		(For National Authority Use Only) COMMENTS
Synthetic or manufacturing route:                      Page(s)		
Description of process:                      Page(s)		
Solvents and reagents:		
Catalysts:		
Purification stages:                      Page(s)		
Drying and milling:                      Page(s)		



Pharmaceutical Critical Summary

Format Q9 – Control of starting materials - Active substance(s) - Scientific data (QC during manufacture): Volume

Name of Company:  Name of Finished Medicinal Product:  Name of Active substance(s)	Tabular format referring to Part 2 C of the Dossier	(For National Authority Use Only)
<b>PART 2 C: CONTROL OF STARTING MATERIALS – ACTIVE SUBSTANCE(S): SCIENTIFIC DATA (QC during manufacture): Volume</b>		
Starting Materials:  Volume    Page(s)	Specifications	(For National Authority Use Only) COMMENTS
Control tests on intermediate products: Volume    Page(s)	Specifications	
Materials used during purification: Volume    Page(s)		
Material	Specifications	

Pharmaceutical Critical Summary

Format Q10 – Control of starting materials - Active substance(s) - Scientific data (development chemistry): Volume

Name of Company:  Name of Finished Medicinal Product:  Name of Active substance(s)	Tabular format referring to Part 2 C of the Dossier	(For National Authority Use Only)
PART 2 C: CONTROL OF STARTING MATERIALS: ACTIVE SUBSTANCE(S): SCIENTIFIC DATA (DEVELOPMENT CHEMISTRY): Volume		
Evidence of chemical structure: Volume Page(s)		(For National Authority Use Only) COMMENTS
Synthetic route: Key intermediates: Elemental analysis (Actual vs Theory): MS: NMR: IR: UV: Other:		
Potential isomerism: Volume Page(s)		
Asymmetric: Carbons: Optical Rotation: Cis-trans isomerism: Threo-erythro isomerism: Other isomers:		
Physico-chemical characteristics: Volume Page(s)		
Solubility: Physical Characteristics: Polymorphism: pKa and pH values: Other:		

Pharmaceutical Critical Summary

Format Q11 – Control of starting materials - Active substance(s) (Analytical development & validation)

Name of Company:  Name of Finished Medicinal Product:  Name of Active substance(s)	Tabular format referring to Part 2 C of the Dossier	(For National Authority Use Only)
<b>PART 2 C: CONTROL OF STARTING MATERIALS: ACTIVE SUBSTANCE(S): (ANALYTICAL DEVELOPMENT &amp; VALIDATION):</b>		
Summary of Analytical Development and Validation Studies  Volume                      Page		(For National Authority Use Only) COMMENTS
Empty space for content		Empty space for content

Pharmaceutical Critical Summary

Format Q12 – Control of starting materials - Active substance(s) – (Impurities)

<p>Name of Company:</p> <p>Name of Finished Medicinal Product:</p> <p>Name of Active substance(s)</p>	<p>Tabular format referring to Part 2 C of the Dossier</p>	<p>(For National Authority Use Only)</p>
<p>PART 2 C: CONTROL OF STARTING MATERIALS. ACTIVE SUBSTANCE(S) – (Impurities): Volume</p>		
<p>Potential impurities arising from the route of synthesis: Volume Page(s)</p>	<p>Test procedures and their limits of detection or limits of quantitation:</p>	
<p>Potential impurities arising during the production and purification: Volume Page(s)</p>	<p>Test procedures and their limits of detection or limits of quantitation:</p>	
<p>Potential impurities/contaminants in substances of vegetable origin (e.g. micro-organisms, pesticides, fumigants, toxic metals): Volume Page</p>	<p>Test procedures and their limits of detection or limits of quantitation:</p>	
<p>Impurities and structural deviants actually found (with indication of amounts): Volume Page(s)</p>		
<p>COMMENTS - (For National Authority Use Only)</p>		

Pharmaceutical Critical Summary

Format Q13 – Control of starting materials - Active substance(s): (Batch Analysis)

Name of Company:  Name of Finished Medicinal Product:  Name of Active substance(s)	Tabular format referring to Part 2 C of the Dossier	(For National Authority Use Only)
PART 2 C: CONTROL OF STARTING MATERIALS. ACTIVE SUBSTANCE(S): (Batch Analysis):		
Batches tested: Volume	Page(s)	(For National Authority Use Only) COMMENTS
Date(s) of manufacture: Place(s) of manufacture: Batch size: Batch (Lot) number: Use of batch (inc. preclinical and clinical testing):		
Results of Tests: Volume Page(s)		
Batch Nos:		
Characteristics:  Identification tests:  Purity tests: — Physical — Chemical — Biological/Immunological:  Other tests:  Assay(s)/potency:		
Reference standard (analytical results): Volume Page(s)		
Characteristics:  Identification tests:  Purity tests: — Physical — Chemical — Biological/Immunological  Other tests:  Assay(s) potency:		

b) Excipients

For excipients described in a pharmacopoeia, the proposed routine batch tests should be summarized. If they are different to those described in a pharmacopoeia a summary of the proof that the excipient meets the quality requirements of the pharmacopoeia must be provided.

For excipients not described in a pharmacopoeia, the specification and routine tests should be summarized. Where the excipient is used for the first time in medicinal product full data must be provided in the dossier of the scientific data on nomenclature, description, manufacture, quality control during manufacture etc. (as for a New Active Substance), and summarized.

Pharmaceutical Critical Summary

Format Q14 – Control of starting materials - Excipients – Specifications and routine test

<p>Name of Company:</p> <p>Name of Finished Medicinal Product:</p> <p>Name of Active substance(s)</p>	<p>Tabular format referring to Part 2 C of the Dossier</p>	<p>(For National Authority Use Only)</p>
<p>PART 2 C: CONTROL OF STARTING MATERIALS. EXCIPIENTS – Specifications and routine test:</p>		
<p>1. Excipients described in a pharmacopoeia: Volume                      Page(s)</p>	<p>(For National Authority Use Only) COMMENTS</p>	
<p>2. Excipients not described in a pharmacopoeia: Volume                      Page(s)</p>		
<p>Characteristics:</p> <p>Identification tests:</p> <p>Purity tests:</p> <ul style="list-style-type: none"> <li>— Physical</li> <li>— Chemical</li> <li>— Biological/Immunological</li> </ul> <p>Other tests:</p> <p>Assay(s) and/or other Potency evaluation:</p>		

Pharmaceutical Critical Summary

Format Q15 – Control of starting materials – Excipients (scientific data)

Name of Company:  Name of Finished Medicinal Product:  Name of Active substance(s)	Tabular format referring to Part 2 C of the Dossier	(For National Authority Use Only)
<b>PART 2 C: CONTROL OF STARTING MATERIALS. EXCIPIENTS (SCIENTIFIC DATA)</b>		
Summary of studies:    Volume    Page(s)		(For National Authority Use Only) COMMENTS



c) Packaging material (immediate packaging)

The specifications and routine tests, the scientific data on the choice and suitability of the packaging material, the batch analyses and analytical results should be summarized. Reference should be made to European Pharmacopoeia or national pharmacopoeia monographs where these exist.

Pharmaceutical Critical Summary

Format Q16 – Control of starting materials - Packaging material (Immediate packaging)

<p>Name of Company:</p> <p>Name of Finished Medicinal Product:</p> <p>Name of Active substance(s)</p>	<p>Tabular format referring to Part 2 C of the Dossier</p>	<p>(For National Authority Use Only)</p>
<p>PART 2 C: CONTROL OF STARTING MATERIALS. PACKAGING MATERIAL (IMMEDIATE PACKAGING)</p>		
<p>Specifications and routine tests: Volume Page(s)</p>	<p>(For National Authority Use Only) COMMENTS</p>	
<p>Type of material:</p> <p>Construction:</p> <p>Quality specification (routine tests and summary of control methods):</p>		
<p>Summary of development studies on packaging materials: Volume Page(s)</p>		
<p>Batch analysis (Analytical results): Volume Page(s)</p>		

## PART 2 C – SPECIFIC MEASURES CONCERNING THE PREVENTION OF THE TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHIES

European Pharmacopoeia Certificates of Suitability or other appropriate documentation in accordance with the current Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathies agents via human and veterinary medicinal products should be provided. Further guidance is also given in the Position paper on the risk assessment of the use of starting materials of ruminant origin in veterinary medicinal products intended for use in ruminant species adopted by the Committee for Veterinary Medicinal Products.

## PART 2 D – CONTROL TESTS ON INTERMEDIATE PRODUCTS

A summary should be provided for any tests that are necessary.

## PART 2 E – CONTROL TESTS ON THE FINISHED PRODUCT

A summary should be provided of the proposed routine product specification and control methods even if these are, or are derived from pharmacopoeial methods.

For active substances of vegetable origin and their preparations, the quantitative determination of all components which may affect therapeutic activity should be summarized.

Pharmaceutical Critical Summary

Format Q17 – Control tests on intermediate products

<p>Name of Company:</p> <p>Name of Finished Medicinal Product:</p> <p>Name of Active substance(s)</p>	<p>Tabular format referring to Part 2 D of the Dossier</p>	<p>(For National Authority Use Only)</p>
<p>PART 2 D: CONTROL TESTS ON INTERMEDIATE PRODUCTS:    Volume                      Page(s)</p>		<p>(For National Authority Use Only) COMMENTS</p>

Pharmaceutical Critical Summary  
 Format Q18 – Control tests on the finished product

Name of Company:  Name of Finished Medicinal Product:  Name of Active substance(s)	Tabular format referring to Part 2 E of the Dossier	(For National Authority Use Only)
PART 2 E: CONTROL TESTS ON THE FINISHED PRODUCT		(For National Authority Use Only)
Product specification and control methods Volume                      Page		
General product characteristics:  Identification tests:  Quantitative determination of active substances:  Purity tests:  Pharmaceutical tests:		
Identification & determination of excipients Volume                      Page		
Approved colouring materials: Volume                      Page   Other additives:		

The expert should summarise the data on the choice and validation of the test procedures. For identification tests the specificity must be stated. For purity tests (e.g. tests for degradation products or related impurities) the specificity limit of detection or limit of quantification must be stated. For quantitative determination (i.e. assay of content of active substance) the specificity, precision, reproducibility, accuracy and linearity/range/sensitivity of the test procedure must be stated and the factors affecting the proposed assay tolerance limits discussed.

Batch analysis results should be summarized.

Pharmaceutical Critical Summary

Format Q19 – Control tests on the finished product (scientific data)

Name of Company:  Name of Finished Medicinal Product:  Name of Active substance(s)	Tabular format referring to Part 2 E of the Dossier	(For National Authority Use Only)
<b>PART 2 E: CONTROL TEST ON THE FINISHED PRODUCT (SCIENTIFIC DATA)</b>		(For National Authority Use Only) COMMENTS
Summary of analytical development and validation studies: Volume    Page(s)		
Batch Analyses: Volume    Page(s)		
Batches Tested: Batch (lot) number: Date(s) of manufacture: Place(s) of manufacture Batch size: Use of batch:		
Results of Batch Analyses: Volume    Page(s)		
Batch Nos:		
Tests:		
Reference Standard		

## PART 2 F – STABILITY

### a) Active substance(s) (where relevant)

The data on the stability of the active substance the batches tested, test methodology, test procedures, results of tests and interpretation of tests should be summarized.



Pharmaceutical Critical Summary  
 Format Q20 – Stability tests on active substance(s)

Name of Company:  Name of Finished Medicinal Product:  Name of Active substance(s)	Tabular format referring to Part 2 F of the Dossier	(For National Authority Use Only)
PART 2 F. STABILITY TESTS ON ACTIVE SUBSTANCE(S) Volume		
Batches tested	Page(s)	
Batch Nos:		
General test methodology	Page(s)	
<u>Accelerated test conditions (temperature °C, % Normal test conditions (temperature °C, %RH, light):</u>  <u>RH, light):</u>		
Test procedures (page(s)		
<u>Assay techniques &amp; validation:</u>		
<u>Determination of degradation products:</u>		
Results of Tests	Page(s)	
Proposed storage conditions and duration of storage to be permitted before retesting		
COMMENTS - (For National Authority Use Only)		

b) Finished product

The data on the finished product stability, the batches tested and the packaging, the test procedures, the characteristics studied, the evaluation method, results of tests, interpretation and the proposed shelf-life and storage conditions, and any ongoing stability studies should be summarized.

Should be also summarized in this part:

Stability in use

Stability if a finished product requires reconstitution or dilution prior to administration

Pharmaceutical Critical Summary  
 Format Q21 – Stability tests on the finished product

Name of Company:	Tabular format referring to Part II F of the Dossier	(For National Authority Use Only)
Name of Finished Medicinal Product:		
Name of Active substance(s):		
PART II F: STABILITY TESTS ON THE FINISHED PRODUCT		
Batches tested and packaging used	Volume	Page(s)
Stability study methods	Volume	Page(s)
Real time studies (temperature °C, %RH, light): Studies under other conditions:		
Characteristics studied	Volume	Page(s)
Physical characteristics: Microbiological characteristics: Chemical characteristics: Packaging characteristics:		
Evaluation methods & validation	Volume	Page(s)
Results of tests	Volume	Page(s)
Interpretation of results	Volume	Page(s)
Proposed shelf-life & storage conditions	Volume	Page(s)
COMMENTS – (For National Authority Use Only)		

Pharmaceutical Critical Summary  
 Format Q22 – In use stability tests

Name of Company:  Name of Finished Medicinal Product:  Name of Active substance(s):	Tabular format referring to Part 2 G of the Dossier	(For National Authority Use Only)
<b>PART 2 G: IN USE STABILITY TESTS</b>		
Batches tested & packaging used	Volume	Page(s)
Stability study methods	Volume	Page(s)
Real time studies (temperature °C, %RH, light): Studies under other conditions:		
Characteristics studied	Volume	Page(s)
Physical characteristics: Microbiological characteristics: Chemical characteristics: Packaging characteristics:		
Evaluation methods & validation	Volume	Page(s)
Results of tests	Volume	Page(s)
Interpretation of results	Volume	Page(s)
Proposed shelf-life & storage conditions		
Volume	Page(s)	
<b>COMMENTS – (For National Authority Use Only)</b>		

## PART 2 G – OTHER INFORMATION

This part is intended for a summary of any information relevant to the pharmaceutical assessment and which has not been covered by any of the previous report. Information on the analytical test procedures used in the metabolism and bioavailability studies and their validation, and a summary of the synthesis of radiolabelled active substance used in metabolic and/or pharmacokinetic studies should be provided.

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 infeed, 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.



## DETAILED AND CRITICAL SUMMARIES ON THE SAFETY AND RESIDUES DOCUMENTATION

When preparing the Safety Critical Summary, it should be remembered that Part III of the dossier is aimed at demonstrating the potential risks to humans and the environmental resulting from use of the product. In the context of human safety, possible effects on the user in charge of treating the animals, those handling treated animals and the consumer of food derived from treated animals should be considered. Although a knowledge of adverse effects in the target species may be useful additional information when assessing the risk for man and the environmental, Part III is not primarily concerned with target species safety, which should be considered in detail in Part IV of the dossier.

The Safety and Residues Critical Summary(s) should be preceded by a product profile. The report(s) are set out according to the sections listed below and further set out in the same sections as the technical information in the dossier

The Summary can cover all sections or different experts can evaluate different sections. All sections are, however, to be covered.

For each section there should be:

- a list of the studies or published papers which are relevant to that aspect of the safety file. All relevant studies must be covered.
- a tabulated summary of each study or published paper, followed by the expert's comments on the quality of the study and his interpretation of the results; a small space should be provided for the national authority to insert additional comments. It is important to avoid duplication. Where tabular formats suffice it is not necessary to duplicate the message in writing.
- a paragraph setting out the expert's overall comments

At the end of the report, the expert should provide an overall conclusion to the safety file, drawing together all the information included in the safety package. This appraisal should include comments on the importance of flawed or missing studies, GLP status of the studies, relevance of findings to man and the environment, relevance of substance tested to the final product, including impurity levels, metabolites, differences in chirality and effects of other substances. The expert should also comment on the outcome of the applicant's user risk assessment including the adequacy of any proposed warnings. Any additional studies, which the expert considers necessary, must be specified.

It should be noted that the need for an MRL is related to the pharmacological activity of the substance (i.e. active substance and excipients). Therefore, the possibility of the need for an MRL for excipients included in the product should be considered. The safety of excipients should be considered in relation to users and consumers.

Suitable formats for use in the safety Critical Summary are shown at the end of these notes on the Safety and Residues Critical Summaries. These may be adapted as necessary to allow more or less space for certain aspects but the overall layout should be respected.

If use is made of detailed published references, in accordance with Article 13 of Directive 2001/82/EC, the expert must show that this is justified.

It is important to note that even when the safety file relies on published literature rather than proprietary data, the same overall layout must be used.

Below are more details on specific sections of the Summary.

**Pharmacodynamics** – studies conducted to establish the pharmacodynamic effects and the mode of action should be evaluated here, **only if they are relevant to the human safety evaluation**. All other aspects should be covered in the clinical expert's report. The following order should be used:

- studies demonstrating desired therapeutic effects (special pharmacodynamics)
- studies demonstrating secondary effects (general pharmacodynamics)
- studies to detect drug interactions

**Pharmacokinetics** – the data on absorption, distribution, biotransformation, excretion and the occurrence of metabolites in laboratory animals should be considered. The relevance should be considered of the methods used, the pharmacokinetic models and the pharmacokinetic parameters. Effects of route of administration, species and sex should be considered.

**Toxicology** – the onset and duration of the toxic effects, the dose-dependency and the reversibility or irreversibility, and all species, route of administration, or sex-related differences should be reviewed and discussed, in particular toxic signs, causes of death, clinical-chemical, haematological, pathological and all other relevant findings. The findings should be discussed in relation to the degree and type of human exposure.

**Single dose toxicity** – the toxic phenomena (both functional and morphological) and their occurrence related to time, dose level, and route of administration, which may result from a single administration of the test substance(s) should be reviewed on the basis of the documentation.

**Repeated dose toxicity** – the toxic phenomena (both functional and morphological) and their occurrence related to time, dose level, and route of administration, which may result from repeated administration of the test substance(s) should be reviewed on the basis of the documentation.

**Tolerance in the target species of animal** – the results of tolerance trials should be discussed here only if the information contained is relevant to the human safety evaluation. All other aspects should be covered by the Critical Summary on the clinical documentation.

**Reproductive toxicity including teratogenicity** – the potential to adversely influence reproductive performance of exposed adults as well as the normal development of their progeny should be reviewed on the basis of the documentation. If teratogenic effects were observed, an interpretation of their significance in view of the safety of the human consumer is necessary.

**Genotoxicity** – the potential of the active substance and/or its relevant metabolites to cause transmissible changes in the genetic material should be assessed on the basis of the documentation and in the light of known structure-activity relationships. The expert should also express his views on the choice and conduct of the tests with respect to their predictive value and the spectrum of potential genotoxic events covered, including the suitability of doses/concentrations tested.

**Carcinogenicity** – the expert should evaluate the potential carcinogenicity of the active substances and/or its metabolites based on the documentation. He should particularly consider the structure of the compound(s) and its(their) relationship to the structure of known carcinogens, data from short-term feeding studies, and any other available information (e.g. covalent binding to cellular macromolecules). In the report, the expert should draw specific attention to observations such as an increase in the incidence of tumours as compared with the untreated control animals, the development



of tumours earlier than in the control animals, the occurrence of types of tumours usually not seen in untreated control animals, the malignancy of tumours, and the appearance of pre-neoplastic lesions. Whenever possible, the (suspected) mechanism of carcinogenicity should be discussed together with the possibility of determining a threshold. The expert should also comment on the suitability of the doses tested, e.g. whether the MTD (Maximum Tolerable Dose) was exceeded.

**ADI (Acceptable Daily Intake)** – the data in the safety dossier should be evaluated with the objective of establishing an ADI if one has not previously been set. The ADI forms the basis for the calculation of the MRLs, which in turn are the basis for the establishment of a withdrawal period, if necessary.

**Other tests** – the expert should comment on the presence or absence of other data as appropriate to the product, e.g. microbiological effects on human gut flora or organisms used in food processing, sensitisation potential or whether any effects on specific organ systems which were identified during repeated dose testing have been adequately followed up. The expert should also comment on the information on metabolites, impurities and excipients.

## **USER SAFETY**

User safety relates to the persons in charge of treating the animals and those handling the products and treated animals.

Some veterinary medicinal products such as tablets and capsules, offer very little opportunity for user contamination, while others with for example dusty formulations or gases which may be inhaled, may offer much greater scope. The expert should comment on the likelihood of exposure, and on the likely degree and extent of exposure and relate this to the toxicity of the drug.

The expert should comment on relevant studies with particular emphasis on specific user groups, for example pregnant women or women of child bearing age or individuals who are known to be sensitive to certain antibiotics. The expert should also comment on physico-chemical properties likely to be relevant to user exposure such as flammability, pH, vapour pressure and oxidising and explosive properties.

The expert should also comment on the likely frequency of exposure as a product intended for occasional use by a pet owner will not present the same degree of risk as one intended for frequent use by a farmer on a large number of animals.

The expert should comment on methods of controlling or limiting user exposure and consider the recommended application/administration of the product in the light of the safety recommendations and warnings proposed on the SPC.

Certain sections of the dossier are particularly relevant to user safety:

**Pharmacokinetics** – data on pharmacokinetics in the target species should be discussed if this is relevant to the user risk assessment.

**Toxicology** – the findings should be discussed in relation to the degree and type of human exposure.

**Single dose toxicity** – the potential risks to the user of the finished product (e.g. by dermal or inhalation exposure, if applicable), should be discussed.

**Reproductive toxicity** – if teratogenic effects were observed, an interpretation of their significance in view of the safety of the user of the product is necessary.

## **ENVIRONMENTAL RISK ASSESSMENT**

For the ecotoxicity section of the dossier it may be appropriate to appoint a different expert to that used for the rest of the safety dossier. A brief critique of the ecotoxicity assessment should be provided, in particular commenting on the assumptions used by the applicant.

For the Phase II assessment a tabulated summary of data would be of value where data are extensive, otherwise a written summary would be useful. The studies included within the dossier should generally be justified in terms of providing the information required for the ecotoxicity assessment.

The studies submitted must always be justified if non-standard protocols are used or if the data provided deviate from current guidance.

The expert should comment whether the environmental safety statements in the Summary of Product Characteristics are adequate.

## **RESIDUES CRITICAL SUMMARY**

The residues Critical Summary should be set out in the same sections as the technical information in the dossier, i.e. B1, B2, B3, etc. For each section there should be:

- a list of the studies which are relevant to that aspect of the safety file
- a tabulated summary of each study, followed by the expert's comments on the quality of the study and interpretation of the results; a small space should be provided for the national authority to indicate agreement or otherwise with the expert's interpretation
- a short paragraph setting out the expert's overall comments on the section

It should be noted that the need for an MRL is related to the pharmacological activity of the substance so that it is possible that excipients should be discussed in this report.

At the end of the report, the expert should provide an overall conclusion to the file, drawing together all the information included in the residue package. This appraisal should include comments on the importance of flawed or missing studies, relevance of findings to man, relevance of substance tested to the final product, including impurity levels/limits, differences in chirality, effects of other substances and range of studies. The expert should also comment on the applicant's proposal for withdrawal period(s). Any additional studies, which the expert considers necessary, must be specified.

Suitable formats for the residues Critical Summary may be adapted from the Safety Critical Summary formats.

It is important to note that even where the residue file relies on published literature rather than proprietary data, the same overall layout must be used.

Below are more details on specific sections of the report.

**Pharmacokinetics** – the data on absorption, distribution, biotransformation, excretion and the occurrence of metabolites in food producing animals should be summarized and assessed in view of the tissue residue characteristics of the veterinary medicinal product. The chemical nature and concentrations of the residues in edible tissues (muscle, liver, kidney, fat, milk, eggs, honey) following use of the product should be discussed. If chemically bound residues have been identified the expert should discuss all available information on mechanisms and reversibility of their formation and their bioavailability following oral ingestion. The expert should also comment on the validity of the methods used in the pharmacokinetic studies including the suitability of any radio-labels.

**Depletion of residues of concern** – the expert should give an opinion on the adequacy of the study design used (route of administration, dose, dosing interval, number of doses given in relation to proposed instruction in the SPC and summarise the time-course (including kinetic parameters) of the depletion of the relevant residues

in edible tissues and should comment on the suitability of the studies to serve as a basis for the calculation of withdrawal periods.

**Maximum residue limits** – if maximum residue limits have already been established under Regulation (EC) No 470/2009<sup>4</sup> of the European Parliament and of the Council the expert should comment on their relevance to the proposed posology.

**Withdrawal periods** – the expert should comment on the applicant's proposal for withdrawal periods, including the method used for calculation.

**Analytical method** – the expert should judge whether the method is adequately described in particular whether the document contains all information relevant to the analyst. The expert should also draw attention to any deficiencies in the use of units, signs, symbols and nomenclature, when compared with international standards.

**Validation of method** – the expert should discuss the strategies followed by the applicant to demonstrate the specificity, accuracy, repeatability, limit of detection, limit of quantification, practicability and applicability of the method, and to eliminate interference from constituents of the biological matrices. The expert should review these characteristics of the method either in accordance with the definitions given in the relevant Note for Guidance or justify and explain the use of equivalent definitions. He should draw attention to any deficiencies in the documentation (e.g. absence of raw data, chromatograms, calibration curves, explanations of the calculations carried out by the applicant, etc.).

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<sup>4</sup> Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council (OJ L152, 16.06.2009, p.11-22)

## SAFETY TABULAR FORMATS

## TABULAR FORMATS FOR THE SAFETY CRITICAL SUMMARY

3A1	Precise identification of the substance	
	Active	Format S1
	Product	Format S2
3A2	Relevant pharmacological studies	
	Pharmacodynamics	Format S3
	Pharmacokinetics in laboratory animals	Format S4
	Method	Format S5
	Results	
	Plasma	Format S6
	Urine and faeces	Format S7
	Tissue distribution	Format S8
	Metabolism	Format S9
	Experts conclusion	Format S10
3A3	Toxicological studies	
	Single dose toxicity	Format S11
	Method	Format S12
	Experts conclusion	Format S13
	Repeat dose toxicity	Format S14
	Method	Format S15
	Results	Format S16
	Experts conclusion	Format S17
	Target species tolerance (summary)	Format S18
	Reproductive toxicity	Format S19
	Effects on reproduction	Format S20
	Results	Format S21
	Experts conclusion	Format S22
	Reproductive toxicity including developmental toxicity	Format S23
	Method	Format S24
	Results	Format S25
	Experts conclusion	Format S26
	Genotoxicity	Format S27
	Study summary	Format S28
	Experts conclusion	Format S29
	Carcinogenicity	Format S30
	method	Format S31
	results	Format S32
	experts conclusion	Format S33
3A4		
	Other requirements	Format S34
	Microbiological properties of residues	Format S35
	Observations in humans	Format S36
	Studies on metabolites etc.	Format S37
	User safety	Format S38
	Environmental risk assessment	Format S39

**Safety Critical Summary – Format S1**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A1: PRECISE IDENTIFICATION OF THE SUBSTANCE (ACTIVE)**

1.1	INN:	
1.2	IUPAC name:	
1.3	CAS number:	
1.4	Classification:	
1.5	Synonyms and abbreviations:	
1.6	Structural formula:	
1.7	Molecular formula:	
1.8	Molecular weight:	
1.9	Degree of impurity:	
1.10	Impurities:	
1.11	Physical properties:	
	Appearance:	
	Melting point:	
	Boiling point:	
	Vapour pressure:	
	pH:	
	Solubility in water:	
	Solubility in organic solvents:	
	Octanol water partition coefficient (Pow):	
	Density:	
	Refractive index:	
	Rotation:	

**Expert's Comments on Active Substance (e.g. expected biological effects resulting from physical properties, relationship to similar compounds, whether well-established or novel, etc.)**

**For National Authority Use Only**

**Safety Critical Summary – Format S2**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A1:      PRECISE IDENTIFICATION OF THE SUBSTANCE (PRODUCT)**

Formulation:

Indications, including Dose Level and Route of Administration:

Flash Point/ Particle Size of Product/Spray Rate/etc. (as applicable):

**Expert's Comments on Formulation (e.g. nature of excipients, MRL status of excipients, flammability of formulation, likely routes of human exposure, frequency of use, quantities handled, etc.)**

**For National Authority Use Only**

**Safety Critical Summary – Format S3**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A2: RELEVANT PHARMACOLOGICAL STUDIES**

2.1. Pharmacodynamics

Summary of Relevant Information

Effect	Location in Dossier
--------	---------------------

Desired therapeutic effects:	
------------------------------	--

Secondary pharmacological effects:	
------------------------------------	--

Mode of action:	
-----------------	--

**Expert's Comments on Relevance to Human Safety**

**For National Authority Use Only**



**Safety Critical Summary – Format S4**

**Name of Company:**

**Name of Product:**

**Active Substance(s):**

**PART 3A2: RELEVANT PHARMACOLOGICAL STUDIES**

**2.2. Pharmacokinetics in Laboratory Animals**

The following pharmacokinetic studies have been carried out:

Species/Strain	Route	Dose Level/ Frequency	Hot or Cold	Absorption, Distribution, Metabolism or Excretion	Study No. or Literature Ref.

**Expert's Comments on Choice of Pharmacokinetic Studies (e.g. relevance of dosing schedule, route of administration, etc.)**

**For National Authority Use Only**

<b>Safety Critical Summary – Format S5</b>
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<b>Name of Company:</b> <b>Name of Product:</b> <b>Active Substance(s):</b>
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<b>PART 3A2: RELEVANT PHARMACOLOGICAL STUDIES</b>
---

2.2. Pharmacokinetics in Laboratory Animals	
Study Summary - Method	Study No.

Study Identification:	Title:	GLP (Yes/No):
	Ref No:	Date:
	Location in Dossier:	
Test System:	Species:	Strain:
	Age:	Sex:
Test Substance:	Name:	Batch No:
	Dose Given (amount/frequency/duration):	Route of Admin:
	Radiolabel/Specific Activity	Vehicle:
Experimental Design:	Time Points:	No. Animals:
	Type and Timing of Sampling:	
Analytical Method:	Type of Method:	LOD and LOQ:
Treatment of Results:	Calculation of Pharmacokinetic Parameters (method/choice of parameters):	
Other Information:		

<b>For National Authority Use Only</b>
--

**Safety Critical Summary – Format S6**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A2: RELEVANT PHARMACOLOGICAL STUDIES**

**2.2. Pharmacokinetics in Laboratory Animals**

Study Summary - Results (plasma) Study No:

Plasma Levels were (µg/l)

Animal No	Time Point 1	Time Point 2	Time Point 3	Time Point 4	Time Point 5	Time Point 6	Time Point 7	Time Point 8	Time Point 9	Time Point 10
1										
2										
3										
n										
Mean										
S.D.										

Animal No	Time Point 11	Time Point 12	Time Point 13	Time Point 14	Time Point 15	Time Point 16	Time Point 17	Time Point 18	Time Point 19	Time Point 20
1										
2										
3										
n										
Mean										
S.D.										

**Expert's Comments on Study (including details of pharmacokinetic parameters calculated)**

**For National Authority Use Only**

**Safety Critical Summary – Format S7**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A2: RELEVANT PHARMACOLOGICAL STUDIES**

2.2. Pharmacokinetics in Laboratory Animals  
 Study Summary - Results (urine and faeces) Study No.

Concentrations in faeces were ( $\mu\text{g}/\text{kg}$ ):

Animal No	Time Point 1	Time Point 2	Time Point 3	Time Point 4	Time Point 5	Time Point 6	Time Point 7	Time Point 8	Time Point 9	Time Point 10
1										
2										
3										
n										
Mean										
S.D.										

Concentrations in urine were ( $\mu\text{g}/\text{l}$ ):

Animal No	Time Point 1	Time Point 2	Time Point 3	Time Point 4	Time Point 5	Time Point 6	Time Point 7	Time Point 8	Time Point 9	Time Point 10
1										
2										
3										
n										
Mean										
S.D.										

**Expert's Comments on Study (including details of pharmacokinetic parameters calculated)**

**For National Authority Use Only**

**Safety Critical Summary – Format S8**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A2: RELEVANT PHARMACOLOGICAL STUDIES**

**2.2 Pharmacokinetics in Laboratory Animals**

Study Summary - Results (tissue distribution) Study No.

Concentrations in tissues were ( $\mu\text{g}/\text{kg}$ ):

Animal No	Liver	Kidney	Skin	Fat	Muscle	Bile				
1										
2										
3										
n										
Mean										
S.D.										

Animal No										
1										
2										
3										
n										
Mean										
S.D.										

**Expert's Comments on Study (including details of pharmacokinetic parameters calculated)**

**For National Authority Use Only**

**Safety Critical Summary – Format S9**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A2: RELEVANT PHARMACOLOGICAL STUDIES**

2.2 Pharmacokinetics in Laboratory Animals

Study Summary - Results (metabolism)	Study No.
--------------------------------------	-----------

Metabolites found were:

Reference	Name

Each metabolite comprised the following percentage of total residue for the samples indicated at the times indicated:

Sample	Metabolite	Time Point 1	Time Point 2	Time Point 3	Time Point 4
Urine	A				
	B				
	C				
	N				
Liver	A				
	B				
	C				
	N				
Etc.					

**Proposed Metabolic Pathway (append if too large)**

**For National Authority Use Only**

**Safety Critical Summary – Format S10**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A2: RELEVANT PHARMACOLOGICAL STUDIES**

2.2 Pharmacokinetics in Laboratory Animals

Expert's Conclusions on Pharmacokinetics

[Empty box for content]

**For National Authority Use Only**

[Empty box for content]

**Safety Critical Summary – Format S11**

<b>Name of Company:</b> <b>Name of Product:</b> <b>Active Substance(s):</b>	
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**PART 3A3: TOXICOLOGICAL STUDIES**

**3.1 Single Dose Toxicity**

The following single dose toxicity studies have been carried out:

Route	Species	Active Substance/Formulation	Study No. or Literature Ref.
Oral			
Dermal			
Inhalation			
Intravenous			
Intraperitoneal			

**Expert's Comments on Choice of Studies (taking into consideration the routes of operator exposure, etc.)**

**For National Authority Use Only**



**Safety Critical Summary – Format S12**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

3.1 Single Dose Toxicity  
 Study Summary – Method Study No.

Study Identification:	Title:	GLP (Yes/No):
	Ref No:	OECD Guideline:
	Location in Dossier:	Date:
Test System:	Species:	Strain:
	Age:	Sex:
Test Substance:	Name:	Batch No:
	Dose(s) Given:	Route of Admin:
	Observation Period:	Vehicle:
Experimental Design:	Type and Timing of Observations/Samples:	No. Animals/Dose:

Results - deaths:															
Dose Group	_mg/kg bw		_mg/kg bw		_mg/kg bw		_mg/kg bw		_mg/kg bw		_mg/kg bw		_mg/kg bw		
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
0 - 6 h															
7 - 24 h															
2 - 7 d															
Total															
Adverse Effects, Including Reversibility															

**Expert's Comments**

**For National Authority Use Only**

**Safety Critical Summary – Format S13**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

3.1 Single Dose Toxicity

Expert's Conclusions on Single Dose Toxicity

[Empty box for expert's conclusions on single dose toxicity]

**For National Authority Use Only**

**Safety Critical Summary – Format S14**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

**3.2 Repeat Dose Toxicity**

The following repeat dose toxicity studies have been carried out:

Route	Species	Duration	Dose Levels	Study No. or Literature Ref.

**Expert's Comments on Choice of Studies (taking into consideration the routes of human exposure, etc.)**

**For National Authority Use Only**

**Safety Critical Summary – Format S15**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

3.2 Repeat Dose Toxicity

Study Summary - Method Study No.

Study Identification:	Title:	GLP (Yes/No):
	Ref No:	OECD Guideline:
	Location in Dossier:	Date:
Test System:	Species:	Strain:
	Age:	Sex:
Test Substance:	Name:	Batch No:
	Dose(s) Given:	Route of Admin:
	Duration of Study:	Vehicle:
Experimental Design:	Nature of Controls:	No. Animals/Dose:
	Type and Timing of Observations/Samples:	

**For National Authority Use Only**

**Safety Critical Summary – Format S16**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

3.2 Repeat Dose Toxicity

Study Summary - Results

Study No.

Food Consumption:

Body Weight:

Haematology:

Clinical Chemistry:

Clinical Observations (including mortality):

Organ Weights:

Gross Pathology:

Histopathology:

Ophthalmoscopy:

Other:

**For National Authority Use Only**

**Safety Critical Summary – Format S17**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

3.2 Repeat Dose Toxicity

Expert's Conclusions on Repeat Dose Toxicity

[Empty box for expert's conclusions on repeat dose toxicity]

**For National Authority Use Only**

**Safety Critical Summary – Format S18**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

**3.3 Target Species Tolerance**

The following target species tolerance studies have been carried out:

Route	Species	Duration	Dose Levels	Location of Summary Table (in Part IV)

Summary of Adverse Effects

**Expert's Comments on Relevance of Studies to the Human Risk Assessment**

**For National Authority Use Only**

**Safety Critical Summary – Format S19**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

3.4 Reproductive Toxicity

3.4.1 Effects on Reproduction

The following reproduction studies have been carried out:

Route	Species	Sex	Duration	Dose Levels	Study No. or Literature Ref.

**Expert's Comments on Choice of Studies**

**For National Authority Use Only**



<b>Safety Critical Summary – Format S20</b>
---

<b>Name of Company:</b>	
<b>Name of Product:</b>	
<b>Active Substance(s):</b>	
<b>PART 3A3: TOXICOLOGICAL STUDIES</b>	
3.4 Reproductive Toxicity	
3.4.1 Effects on Reproduction	
Study Summary - Method	Study No.

Study Identification:	Title:	GLP (Yes/No):
	Ref No:	OECD Guideline:
	Location in Dossier:	Date:
Test System:	Species:	Strain:
	Age:	Sex:
Test Substance:	Name:	Batch No:
	Dose(s) Given:	Route of Admin:
	Duration of Dosing:	Vehicle:
Experimental Design:	Nature of Controls:	No. Animals/Dose:
	Type and Timing of Observations/Samples:	

<b>For National Authority Use Only</b>
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**Safety Critical Summary – Format S21**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

3.4 Reproductive Toxicity  
3.4.1 Effects on Reproduction  
Study Summary - Results | Study No.

Food Consumption:

Body Weight of Adults:

Clinical Observations (including mortality):

Weight of Litter:

Number of off-spring (live and dead):

Sex of off-spring:

Gross Pathology of Adults:

Gross Pathology of off-spring:

Histopathology of Adults:

Other:

**For National Authority Use Only**



**Safety Critical Summary – Format S23**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

3.4. Reproductive Toxicity

3.4.2. Study of developmental toxicity

The following studies have been carried out:

Route	Species	Sex	Duration	Dose Levels	Study No. or Literature Ref.

**Expert's Comments on Choice of Studies**

**For National Authority Use Only**

<b>Safety Critical Summary – Format S24</b>
---

<b>Name of Company:</b> <b>Name of Product:</b> <b>Active Substance(s):</b>
---

3.4 Reproductive Toxicity	
3.4.2. Study of developmental toxicity	
Study Summary - Method	Study No.

Study Identification:	Title:	GLP (Yes/No):
	Ref No:	OECD Guideline:
	Location in Dossier:	Date:
Test System:	Species:	Strain:
	Age:	Sex:
Test Substance:	Name:	Batch No:
	Dose(s) Given:	Route of Admin:
	Duration of Dosing:	Vehicle:
Experimental Design:	Nature of Controls:	No. Animals/Dose:
	Type and Timing of Observations/Samples:	

<b>For National Authority Use Only</b>
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**Safety Critical Summary – Format S25**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

3.4. Reproductive Toxicity  
3.4.2. Study of developmental toxicity  
Study Summary - Results | Study No.

Food Consumption:

Body Weight:

Clinical Observations (including mortality):

Gross Pathology (with emphasis on reproductive system):

Weight of Foetuses:

Sex of Foetuses:

Gross Appearance of Foetuses:

Visceral Effects:

Skeletal Effects:

Other:

**For National Authority Use Only**

**Safety Critical Summary – Format S26**

**Name of Company:**

**Name of Product:**

**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

3.4 Reproductive Toxicity

3.4.2. Study of developmental toxicity

Expert's Conclusions on Embryotoxicity/Foetotoxicity

Empty box for expert's conclusions on embryotoxicity/foetotoxicity.

**For National Authority Use Only**

Empty box for national authority use only.

**Safety Critical Summary – Format S27**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**  
**3.5 Genotoxicity**

**The following mutagenicity studies have been carried out:**

Type of Study	Study No. or Literature Ref.
Gene mutations in bacterial cells	
Chromosome aberrations in mammalian cells ( <i>in vitro</i> )	
Gene mutations in eukaryotic cells	

**Expert's Comments on Choice of Studies:**

**For National Authority Use Only**



**Safety Critical Summary – Format S28**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

3.5 Genotoxicity

Study Summary

Study Identification:	Title:	GLP (Yes/No):
	Ref No:	OECD Guideline:
	Location in Dossier:	Date:
Test System:	Species/Cell Type:	Strain:
Test Substance:	Name:	Batch No:
	Concentration(s) Used:	Vehicle:
Experimental Design:	Control Substance (no metabolic activation):	Duration of Exposure:
	Control Substance (with metabolic activation):	

Summary of Results:

**Expert's Comments and Conclusion Regarding Study**

**For National Authority Use Only**

**Safety Critical Summary – Format S29**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

3.5 Genotoxicity

Expert's Conclusions on Genotoxicity

[Empty box for expert's conclusions on genotoxicity]

**For National Authority Use Only**

**Safety Critical Summary – Format S30**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

**3.6 Carcinogenicity**

The following carcinogenicity studies have been carried out:

Route	Species	Duration	Dose Levels	Study No. or Literature Ref.

**Expert's Comments on Choice of Studies or Justification for Absence of Studies**

**For National Authority Use Only**

**Safety Critical Summary – Format S31**

<b>Name of Company:</b>	
<b>Name of Product:</b>	
<b>Active Substance(s):</b>	

**PART 3A3: TOXICOLOGICAL STUDIES**

3.6 Carcinogenicity

Study Summary - Method

Study Identification:	Title:	GLP (Yes/No):
	Ref No:	OECD Guideline:
	Location in Dossier:	Date:
Test System:	Species:	Strain:
	Age:	Sex:
Test Substance:	Name:	Batch No:
	Dose(s) Given:	Route of Admin:
	Duration of Study:	Vehicle:
Experimental Design:	Nature of Controls:	No. Animals/Dose:
	Type and Timing of Observations/Samples:	

**For National Authority Use Only**

**Safety Critical Summary – Format S32**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

3.6 Carcinogenicity

Study Summary - Results

Food Consumption:

Body Weight:

Haematology:

Clinical Observations (including mortality):

Organ Weights:

Gross Pathology:

Histopathology:

Summary of Tumour Incidence:

Expert's Interpretation of Findings:

**For National Authority Use Only**

**Safety Critical Summary – Format S33**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A3: TOXICOLOGICAL STUDIES**

3.6 Carcinogenicity

Expert's Conclusions

[Empty box for expert's conclusions]

**For National Authority Use Only**

**Safety Critical Summary – Format S34**

**Name of Company:**

**Name of Product:**

**Active Substance(s):**

**PART 3A4: OTHER REQUIREMENTS**

4.1 Special Studies including specific target organ toxicity (e.g. immunotoxicity, endocrine function tests, liver and renal function tests, effects on enzymes, neurotoxicity, sensitisation, skin and eye irritation, inhalation toxicity, mechanistic studies, relay toxicity studies, etc. as appropriate)

The following special studies have been carried out:

**Expert's Comments on Relevance of Special Studies or Omission of Studies Needed**

**For National Authority Use Only**

**Safety Critical Summary – Format S35**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A4: OTHER REQUIREMENTS**

4.2 Microbiological Studies (for compounds with antimicrobial activity) addressing potential effects on the human gut flora and the potential effects on the micro-organisms used for industrial food processing

The following studies have been carried out:

**Expert's Comments on Choice of Studies**

**For National Authority Use Only**



**Safety Critical Summary – Format S36**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A4: OTHER REQUIREMENTS**

4.3 Observations in Humans

Summary of Information Available

Dosage (amount, frequency, route, reason)	Observations	Reference/Location in Dossier

**Expert's Comments on Relevance of Observations in Humans**

**For National Authority Use Only**

**Safety Critical Summary – Format S37**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A4: STUDIES OF OTHER EFFECTS**

**4.4 DEVELOPMENT OF RESISTANCE**

The following studies have been carried out:

**Expert's Comments on Choice of Studies**

**For National Authority Use Only**

**Safety Critical Summary – Format S38**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A4: OTHER REQUIREMENTS**

**4.5 USER SAFETY**

**For National Authority Use Only**

**Safety Critical Summary – Format S39**

**Name of Company:**  
**Name of Product:**  
**Active Substance(s):**

**PART 3A4: OTHER REQUIREMENTS**

**4.6 ENVIRONMENTAL RISK ASSESSMENT**

[Empty box for Environmental Risk Assessment content]

**For National Authority Use Only**



DETAILED AND CRITICAL SUMMARIES ON EFFICACY DOCUMENTATION

The Efficacy Detailed and Critical Summary should be preceded by a product profile. The Report should be divided into several sections:

### **Introduction**

An introduction outlining the objective of the efficacy studies the essentials of the clinical problem itself and its background.

### **Relevant pre-clinical data**

The mode of action of the product should be described if known. In respect of antibacterials and antiparasitics products the effect of the active substance on target pathogens should be outlined. Particular attention should be given to the characterisation of organisms used including the origin of test organisms and the date of isolation. Information should also be given concerning the development of resistance and its importance to the clinical efficacy of the product. The main effect of the active substances on body organs and systems should be described in relation to the expected effects of the product and its therapeutic index. The pharmacokinetic profile of the active ingredient in the product in the target species should be described. If clinically relevant, the bioavailability, distribution, metabolism and elimination of the active substance should be described. Tmax, Cmax and the AUC values should be stated and where relevant, the effect of repeated dose treatment discussed in relation to the inter-dose intervals.

With fixed-dose combination products, it is essential that the Expert should comment on the justification of the formulation and on any possible interactions.

### **Tolerance**

The adequacy of the investigation conducted in support of the tolerance of the product for the target species should be assessed. Both local and systemic tolerance should be evaluated and a comment given concerning the therapeutic index and safety of use. Due regard should be given to the excipients in the formulation which may effect the tolerance of the product. A tabulated summary of each tolerance study or published paper should be given a comment on the quality of the study and whether the study has been conducted in accordance with Good Laboratory Practice should be made. Where studies on laboratory animals have been conducted in support of the target species, the relevance with the model used should be discussed. Where tabular formats suffice, it is not necessary to duplicate the message in writing.

### **Clinical Data**

A tabular summary of each clinical efficacy study or published paper should be provided. In each case, a comment should be made on the suitability of the trial design, the method of randomisation, the inclusion/exclusion criteria, the statistical method used and the end points used for efficacy testing. The evaluation should consider, in particular, the efficacy parameters chosen, the scoring system and the characteristics of the animals used in the studies in comparison to the target population. The number of animals treated with the test product and with control products should be identified in respect of each indication for the product. The suitability of the controls product used should be discussed. The formulation of the test product used in each study as well as the doses submitted and the route of administration should be compared with that recommended for usage. A comment should be given on whether the studies had been conducted in accordance with Good Clinical Practice. An assessment should be made whether efficacy has been shown or is considered satisfactory in the categories of target animal species which the product is indicated (e.g. young animals, lactating animals) and whether any possible interactions likely to be incurred under normal field use have been investigated. The adequacy of the dose finding in dose confirmation studies should also be assessed.

An opinion should be given on the suitability of the statistical methods used and on the validity of any statistical analysis made by the applicant.

**Literature /bioequivalence data**

The relevance of any published scientific literature used in the application should be evaluated, particularly where these are used in the place of trials carried out with the actual product under assessment. In respect of bioequivalence studies, particular attention should be paid to the design of the study and the suitability of the reference product chosen. In the case of a generic application, comment should be made on whether the requirements for bioequivalence have been met.

**Risk/ Benefit ratio**

The risk benefit balance of the product must be evaluated in comparison with appropriate recognised therapy to adjudge whether the effective dosage has been adequately defined and the dosage regimen validated. Comment should be made on whether the clinical trials take in account of the geographical conditions, animal management systems, disease conditions etc in Member States where the product is to be authorised and an opinion given on how the product would be expected to perform in these circumstances. Comment should also be made on whether the indication(s) claimed in the Summary of Product Characteristics had been adequately demonstrated in each target species and whether the exclusion criteria used in the clinical trials are reflected in the claims, indications, contraindications and precautions. Any observed side effects or suspected adverse reactions should also be addressed in relation to the use of the product and completeness of the warnings, precautions and contraindications of the SPC and package leaflet.

**Conclusion**

An overall conclusion should be provided based not only on the data presented but on the experience of the expert and his/her knowledge of scientific publications. Any references used by the Expert should be presented in an appendix to the report.





# **TECHNICAL DOCUMENTATION**



## 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.

In the case 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 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.

### 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.

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 Pharmaceuticals**

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 pharmaceuticals. 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 Health Care 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.

Note: it is the responsibility of the Applicant for a marketing authorisation to ensure that complete information is submitted to the authorities. The applicant must therefore consult and work together with the person submitting a separate master file to ensure all relevant information required as part of the Part 2 of the dossier and in the Part 2 critical summary. Where confidential data on the manufacture of the active substance is supplied separately, a separate critical summary must be provided.

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.

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**

The origin, including geographical region, 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.

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, 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 Health Care, 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 according to Guideline 3AQ11a as indicated in the table below. The test which are carried out routinely on each batch of finished product should be specified. The frequency of the tests which are not carried out routinely shall be stated. Release limits shall be indicated.

#### **SPECIFICATIONS OF THE MEDICINAL PRODUCT**

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	Methods and Acceptance Limits
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Characteristics	of the medicinal product up to the end of shelf life	of the medicinal product at release
1. Characteristics of the pharmaceutical form	Indicate with an asterisk the specification limits which may require updating in the light of experience acquired after the first “n” production batches	
2. Identification and assay of active substance		
3. Purity tests		
4. Excipient: Identification for example of colorants, preservatives, limit values of preservatives etc.		

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. 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  $\pm 5\%$  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**

This part is intended for a summary of any information relevant to the pharmaceutical assessment and which has not been covered by any of the previous report. Information on the analytical test procedures used in the metabolism and bioavailability studies and their validation, and a summary of the synthesis of radiolabelled active substance used in metabolic and/or pharmacokinetic studies should be provided.

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 infeed, 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**

Part III of the dossier is aimed at demonstrating the potential risks for man and the environment resulting from use of the product. In the context of human safety, it is necessary to consider possible effects on people using the product, handling treated animals and consuming food products derived from treated animals. Although a knowledge of adverse effects in the target species may be useful additional information when assessing the risk for man and the environment, Part 3 is not primarily concerned with target species safety, which should be considered in detail in Part 4 of the dossier.

Studies submitted to demonstrate safety of chemicals to man and the environment must be conducted and reported in accordance with Good Laboratory Practice (GLP).

### **PART 3A: SAFETY DOCUMENTATION**

The safety documentation should be presented in a separate file. It is helpful if the environmental safety data are bound separately from the remainder of the safety data if a Phase II assessment is required. The first volume of the file should contain a general index highlighting the location (volume and page number) of the documents contained in the file. Subsequent volumes should contain an index of the contents of that volume. Documents should be presented as dated and signed reports from named laboratories. Summaries not accompanied by the individual data will not be accepted as valid documentation.

Relevant data obtained from the open literature should always be included in the documentation. Copies of published data should be appended to the proprietary data. All proprietary data should be discussed in conjunction with the data from the open literature.

If the application relates to food producing species and if the active substance(s) of the veterinary medicinal product concerned has(ve) previously been evaluated in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council, this should be clearly stated in an introduction to the safety documentation. Except in the case of applications submitted pursuant to points Article 13 of Directive 2001/82/EC, full copies of all the documents submitted in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council must be included in the documentation. Throughout, the documentation the applicant should clearly identify those documents which were submitted in accordance with that Regulation and any new documentation which is submitted in support of the application for marketing authorisation.

If no MRLs have been established by the Community in respect of the active substance(s) concerned, and if the product is for use in food-producing species and no MRLs have been established by the Community in respect of the active substance(s), the applicant should check whether the substances appear on the EMEA list of substances for which valid MRL applications have been received. If not an MRL application must be submitted 6 months prior to the marketing authorisation application.

It should be noted that the need for MRL is related to the pharmaceutical activity of the substance (i.e. active substance and excipients). Therefore, the possibility of the need for an MRL for excipients included in the product should be considered.



Further guidance on the requirements in respect of MRLs may be found in Volume 8 of The Rules Governing Medicinal Products in the European Community – Establishment by the European Community of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin.

## **PART 3B: RESIDUE DOCUMENTATION**

The residue documentation should be presented in a separate file. The first volume of the file should contain a general index highlighting the location (volume and page number) of the documents contained in the file. Subsequent volumes should contain an index of the contents of that volume. The sequence of the documentation should follow the order given below.

Documents should be presented as dated and signed reports from named laboratories. Summaries not accompanied by the individual data will not be accepted as valid documentation.

Relevant data obtained from the open literature should always be included in the documentation. Copies of published data should be appended to the proprietary data. All proprietary data should be discussed in conjunction with the data from the open literature.

If no MRLs have been established by the Community in respect of the active substance(s) concerned, and if the product is for use in food-producing species and no MRLs have been established by the Community in respect of the active substance(s), the applicant should check whether the substances appear on the EMEA list of substances for which valid MRL applications have been received. If not an MRL application must be submitted 6 months prior to the marketing authorisation application.

### **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 the 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 the 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 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.

Specific guidance is provided in Volume 6C of the Notice to Applicants ([http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-6/newdoc/vol6c\\_env\\_risk\\_gmo\\_200603.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-6/newdoc/vol6c_env_risk_gmo_200603.pdf)).

## **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 Regulation (EC) No 470/2009 of the European Parliament and of the Council 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.

#### **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 TRIALS**

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.

A written summary is essential for large, complex clinical documentation. Such documentation may be contained in numerous volumes, and a 1-2 page summary at the beginning of each volume, which details its contents and includes an index of that volume, is particularly helpful. These short summaries can then form the basis for the overall summary.

For further clarification, an overview table of clinical studies should precede the written summary. This table should indicate the type of studies which have been undertaken, i.e. bioequivalence, bioavailability, dose determination, dose confirmation, laboratory studies or clinical field trials, the numbers of each type of study and the numbers of animals which participated in each type of study.

### **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 the 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 contraindications 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, summarized 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 summarized 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 overdose, 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.

**IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS**



## INTRODUCTION

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 of the Directive and in relevant guidelines.

The application dossier for immunological products has additional information, which are only relevant for this type of medicinal products. The requirements for immunologicals are detailed in the following pages. For each reference, paragraphs from the pharmaceutical section have been duplicated in this Section where they are relevant.

Part 1 – Summary of the dossier

Part 2 – Chemical, Pharmaceutical and biological/microbiological information

Part 3 – Safety tests

Part 4 – Efficacy tests

Administrative documentation

Part 1 is divided into 3 sub-sections. Parts 1 A, 1 B and 1 C are always required. Part 1 B must be in the language(s) of the Member State(s) concerned or in all Community languages for centralised applications. Parts 1 A and 1 C should be submitted in the language of the Member State concerned if so requested in Chapter 7 of Volume 6A of The Notice to Applicants.

- Part 1 A consists of the administrative data, packaging, samples or mock-ups, manufacturing and marketing authorisations applied for or obtained elsewhere.
- Part 1 B consists of the proposed Summary of Product Characteristics (SPC), label and package leaflet in accordance with Articles 14, 58(1) to (3) and 61 of Directive 2001/82/EC.
  - Part 1 B1 Summary of Product Characteristics (SPC)
  - Part 1 B2 Proposals for Packaging, Labelling & Package Leaflet
  - Part 1 B3 SPCs already approved in the Member States
- Part 1 C consists of the Detailed and Critical Summaries and their tabular formats. There should be separate Detailed and Critical Summaries on the chemical/pharmaceutical/biological, safety/residues and pre-clinical/clinical documentation. With regard to safety/residues, it is preferable for the toxicology, user safety, environmental and residues aspects of the Detailed and Critical Summaries to be presented separately. Target animal safety should be presented separately within the pre-clinical/clinical Detailed and Critical Summaries.

## **Technical documentation**

Parts 2, 3, and 4 of the application dossier consist of the chemical, pharmaceutical and biological documentation, the safety and residue documentation, and the efficacy documentation. A written summary for the relevant sections of Part 3 and Part 4 may facilitate mutual recognition by concerned Member States, and may also assist in the consideration of an application by the members of the Committee for Veterinary Medicinal Products of the European Agency for the Evaluation of Medicinal Products

## REQUIREMENTS FOR IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

### 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 or mock-ups, 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.

The [application form](#) to be used is available for downloading from the Commission's website.

#### 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 Directive 2001/82/CE amended.

A proposed labelling text for the immediate and outer packaging shall be provided in accordance with Title V of the Directive, together with a package leaflet where one is required pursuant to Article 61. In addition the applicant shall provide one or more 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**

### **1. GENERAL**

It is important to emphasise that well prepared Detailed and Critical Summaries greatly facilitate the task of the competent authority in evaluating the dossier and contribute towards the speedy processing of applications. For these reasons particular care should be taken in the preparation of Detailed and Critical Summaries, following the guidance on the preparation of Detailed and Critical Summaries given below.

Authors of Detailed and Critical Summaries must be chosen on the basis of their qualifications and their recognised expertise in the field concerned. The experts should preferably not have been personally involved in the conduct of the tests included in the dossier.

Each Detailed and Critical Summary should consist of:

- an abbreviated product profile;
- a critical evaluation of the dossier;
- the opinion of the expert as to whether sufficient guarantees have been provided as to the suitability of the product for its proposed use;
- a summary of all the important data;
- the signature of the expert and the place and date of the report's issue;
- the expert's *curriculum vitae* and a declaration of the expert's professional relationship to the applicant.

The product profile should include the following key points:

- a) type of application, e.g.
  - a new active substance;
  - a product essentially similar to one already on the market;
  - a new combination of known active substances;
  - a new method of manufacture;
- b) name of product
  - name of the immunological veterinary medicinal product, including the international non-proprietary name(s) of the active substance(s);
- c) pharmaceutical form
  - the pharmaceutical form (including route of administration), strength (e.g. potency/antigen content/viral titre), sales presentation (eg. syringe, vial, ampoule);
- d) indications
  - target species;
  - the therapeutic indications (if necessary for each target species);
- d) precautions
  - significant precautions and warnings for the target species, other species, those administering the product;



- e) marketing authorisations/pharmacovigilance
  - a list of marketing authorisations already issued in other countries, and those for which applications have been submitted;
  - a list of any measures resulting from pharmacovigilance.

It is essential to note that the Detailed and Critical Summaries must include a critical evaluation and bring out all the data relevant to the evaluation. The expert is expected to take and defend a clear position on the final product, in the light of current scientific knowledge. A simple factual summary of the information contained in the application is not sufficient and the Detailed and Critical Summaries must not be a repetition of other parts of the dossier, although important data will need to be summarized in the Detailed and Critical Summaries in some form.

By selecting the expert, the applicant delegates to the expert the task of preparing a critical view of the relevant part of the dossier on his behalf. It is, however, the applicant himself who remains primarily responsible vis-à-vis the competent authorities for the whole dossier, including the Detailed and Critical Summaries.

More detailed guidance on the preferred form for summary data in Detailed and Critical Summaries is provided below under the headings of Production and control, Safety and Efficacy. Both Detailed and Critical Summaries and summarized tables must contain precise references to the information contained in the main documentation. If experts wish to supplement their report by reference to additional literature, they must indicate clearly that the applicant has not included this information in the relevant part of the dossier.

Where relevant Community guidelines on the conduct of tests, studies and trials on a medicinal product exist, these should be taken into consideration when Detailed and Critical Summaries are prepared. Any deviation from guidelines should be discussed and justified. In particular, the experts should give a justification for the statements in the proposed summary of product characteristics (SPC), taking into account the submitted data and the current SPC guidelines.

For applications submitted through the mutual recognition procedure, the Detailed and Critical Summaries and summary tables must cover all the data submitted in support of the application, including any data collected after the granting of the initial authorisation.

## DETAILED AND CRITICAL SUMMARIES ON ANALYTICAL DOCUMENTATION

For the production and control part of the dossier for immunological veterinary medicinal products including medicinal products which contain or consist of genetically modified organisms a written summary of no more than 30 pages in length should be provided. Page references should be made to the appropriate volume and page of the Part II documentation or other relevant Parts of the full dossier. Attached to the Detailed and Critical Summaries should be a summary in tabular form of the data and where it can be found in the dossier. For immunological veterinary medicinal products containing or consisting of genetically modified organisms (GMOs) further guidance on environmental risk assessment is available in Volume 6C of the Notice to Applicants

([http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-6/newdoc/vol6c\\_env\\_risk\\_gmo\\_200603.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-6/newdoc/vol6c_env_risk_gmo_200603.pdf)).

It is assumed, since the analytical expert has written and signed his/her Detailed and Critical Summaries, that he/she is convinced that the product as developed is of the appropriate quality and that the proposed control tests and limits are those appropriate to ensure that the routinely manufactured batches continue to meet this quality requirement. The analytical expert should therefore not state this as his/her conclusion but instead critically review and discuss the elements of the dossier and data provided which led him/her to this view.

Some elements which might be included here are:

1. Composition of the product

A discussion of the differences between the composition of the immunological veterinary medicinal products used in the safety and efficacy data and that to be marketed and the significance of such differences (particularly in relation to release and end-of-shelf life specifications for the active substance(s), the adjuvant or diluent used).

2. Development pharmaceuticals

A discussion of the choice of the strain of organism used in the product and its relevance to the epizootic situation within the Community. For genetically-modified organisms a justification should be provided for the methods used and the stability of the resultant changes. The choice and concentration of any adjuvant, stabiliser or diluent used should be discussed.

The choice and concentration of preservatives should be discussed and shown to be optimised for their intended purpose in the product and the pack size (e.g multi-dose packs). In particular the results of preservative efficacy testing in relation to product storage, reconstitution, dilution and use should be discussed.

4. Method of preparation

A discussion as to how the particular manufacturing method and in-process control tests will consistently guarantee batches of product of the desired quality and that all individual dosage units within the batch are also acceptable.

5. Process validation

A discussion as to how the data gives the required assurance of suitable product quality.

6. Control of pharmacopoeial active substance(s)

A discussion of any deviations from the pharmacopoeia.

7. Control of non-pharmacopoeial active substance(s)  
This discussion should include the suitability of the substances of biological origin used in the product and its manufacture. The data discussed should include the tissue, species and country of origin the tests/measures taken to ensure freedom from extraneous agents etc.
8. Excipients  
A discussion of the suitability of the specification proposed. For new excipient(s) full data is needed and there should be a cross-reference to the data in the safety Detailed and Critical Summaries.
9. Packaging material (immediate packaging)  
A discussion of the results of the studies on suitability of the packaging material in relation to proposed storage conditions and use of the product (e.g. moisture protection). Also a discussion of the specification and batch results.
10. Control tests on intermediate products  
Where some tests on the finished product are not proposed to be carried out routinely because intermediate products are controlled, this should be discussed and justified.
11. Control tests on the finished product  
A discussion of the suitability of the proposed specification and control methods. The tests and limits (particularly for the quantitative determination of active substance(s) and identity tests) should be justified in relation to the results of the analytical validation studies, the batch analyses, and any information on production variability (incl. results of process validation studies). The results of production batch analyses should be compared to demonstrate reproducibility of the manufacturing process for the product.
12. Stability of the active substance(s)  
A discussion of the conclusions as to the variability of batches of antigen in stability, the most appropriate storage conditions, and the duration of storage before retesting to check compliance with specification.
13. Stability of the finished product  
A discussion of the results of the stability trials and analysis of the data. The method of calculation or estimation of the shelf-life should be explained together with a justification for the recommended storage conditions. The basis for the recommendations on storage during marketing and use should be given.
14. Environmental risk assessment  
The safety of the product with respect to other animals and the environment should be assessed. Particular reference should be made to studies of spread of antigens or organisms included in the immunological veterinary medicinal product, reversion to virulence and other factors which may influence the safe use of the product.
15. Reference list  
A list of references used, in addition to those contained in the dossier, should be given and stated in accordance with internationally accepted standards of the 1979 Vancouver Declaration on "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" or the system used in "Chemical Abstracts".
16. Information on the qualifications and experience of the analytical expert  
The qualifications and experience of the expert should be briefly summarized. Although only one expert may assume responsibility for the report other experts may contribute to it.

## DETAILED AND CRITICAL SUMMARIES ON SAFETY DOCUMENTATION

For the safety Detailed and Critical Summaries for a dossier for immunological veterinary medicinal products a written summary of no more than 30 pages in length should be provided. Attached to the Detailed and Critical Summaries should be a summary in tabular form of the data and where it can be found in the dossier. Page references should be made to the appropriate volume and page of the Part II documentation or other relevant Parts of the full dossier.

It is assumed, since the safety expert has written and signed his/her Detailed and Critical Summaries, that he/she is convinced that the product as developed, is safe and that the proposed SPC is sufficient to ensure that the product is used safely. The safety expert should therefore not state this as his/her conclusion but instead critically review and discuss the elements of the dossier and data provided which led him/her to this view.

Some elements which should be included here are:

1. The relevance of the data to the product to be marketed;
2. The completeness of the safety data for each of the classes and species for which the product is intended;
3. The evidence for safety in these animals;
4. The safety or risks to the operator or of waste materials emanating from the use of the product;
5. The suitability of the warnings on the SPC and product literature in the light of the results obtained.

It is preferable to provide for the analytical Detailed and Critical Summaries to cover the environmental risk assessment for immunological veterinary medicinal products with respect to risks related to the antigen or organisms included, including if relevant for genetically modified organisms.

## DETAILED AND CRITICAL SUMMARIES ON EFFICACY DOCUMENTATION

For the efficacy Detailed and Critical Summaries for a dossier for immunological veterinary medicinal products including medicinal products, which contain or consist of genetically modified organisms a written summary of no more than 30 pages in length should be provided. Attached to the Detailed and Critical Summaries should be a summary in tabular form of the data and where it can be found in the dossier. Page references should be made to the appropriate volume and page of the Part 2 documentation or other relevant Parts of the full dossier.

It is assumed, since the efficacy expert has written and signed his/her Detailed and Critical Summaries, that he/she is convinced that the product as developed is of the appropriate quality and that the claims/indications given on the SPC are supported by the data. The efficacy expert should therefore not state this as his/her conclusion but instead critically review and discuss the elements of the dossier and data provided which led him/her to this view.

Some elements which should be included here are:

1. The relevance of the data to the product to be marketed;
2. The completeness of the efficacy data for the recommended uses (eg. route of administration, dosage regimen etc.);
3. How far the evidence presented supports the claims made for the product;
4. The substantiation of any stated or implied claims regarding nature, strength and duration of immunity.

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 summarized 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.

## TECHNICAL DOCUMENTATION

## **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 compliance 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, oligonucleotide sequences of plasmid vector in cells, plasmid used for co-transfection, 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 Health Care, 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 physicochemical 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 product 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 to be used for food producing animals, these studies must 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.

## **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.

Specific guidance is provided in Volume 6C of the Notice to Applicants ([http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-6/newdoc/vol6c\\_env\\_risk\\_gmo\\_200603.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-6/newdoc/vol6c_env_risk_gmo_200603.pdf)).

## **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 epizootological 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.



## 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 bioequivalence 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.

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 the 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.

## REQUIREMENTS FOR MARKETING AUTHORISATION APPLICATIONS FOR PARTICULAR VETERINARY MEDICINAL PRODUCTS S

### 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 was introduced.

A Vaccine Antigen Master File is 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 the vaccine. 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.

#### 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.

### 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) of the Directive.

#### 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 the Directive with the following specification, without prejudice to the provisions of Regulation (EC) No 470/2009 of the European Parliament and of the Council 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.