The rules governing medicinal products
in the European Union

Volume 6B

Notice to applicants

Veterinary medicinal products

Presentation and content of the dossier

2004

EUROPEAN COMMISSION
Directorate-General Enterprise
Pharmaceuticals: Regulatory framework and market authorisations

FOREWORD

This Notice to Applicants (NTA) has been prepared by the European Commission, in consultation with the competent authorities of the Member States and the European Agency for the Evaluation of Medicinal Products. This Notice has no legal force and does not necessarily represent the final views of the Commission. In case of doubt, therefore, reference should 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 presents the harmonised views of the Member States on how those requirements may be met.

The previous Notice to Applicants (Volume VB in the series of *The rules governing medicinal products in the European Union*) was published in January 1995. A partially revised version was issued in May 1996. The new volume 6A concerns the procedures for marketing authorisation of veterinary medicinal products and updates the previous volumes. The procedures for applications for a marketing authorisation have been updated according to centralised and mutual recognition procedures. The resulting size of the NTA has meant that is has been divided into parts:

— Volume 6A dealing with procedures for marketing authorisation;

— Volume 6B dealing with the presentation and content of the application dossier.

The Community application dossier, which should be submitted in either a national or Community procedure (i.e. to competent authorities of the Member States and the European Agency for the Evaluation of Medicinal Products), consists of administrative information and the necessary demonstration of quality, safety and efficacy of the veterinary medicinal product.

The current volume 6B is concerned with the structure and content of the application dossier of veterinary medicinal products (Parts I, II, III, IV) and is divided in two sections: Pharmaceuticals and Immunologicals. It 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. 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 Article 12 of that Directive.

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GENERAL INFORMATION

The Community application dossier, to be submitted in either a Community or national procedure (i.e. to competent authorities of the Member States or the European Agency for the Evaluation of Medicinal Products), consists of administrative information and the necessary demonstration of quality, safety and efficacy of the veterinary medicinal product.

For abridged applications submitted in accordance with Article 13(1) of Directive 2001/82/EC, applicants should clearly indicate whether the application is made under point i, ii or iii.

Each volume of the dossier should be sequentially paginated throughout, in Arabic numerals, legible and suitably bound. Each volume should be clearly identified. Particular care should be given to proper and consistent cross-referencing throughout the dossier.

For information on the number of copies required and the addresses for submission, please see Chapter 7 of Volume 6A of *The rules governing medicinal products in the European Union.*

If spectra or photographic material are supplied in the dossier, **legible** copies and photographs should be supplied in each copy submitted.

Full copies of all bibliographical references should be provided, translated if necessary.

PHARMACEUTICALS (NON-IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS)

INTRODUCTION

The application dossier for pharmaceutical products is presented in four parts.

Part 1 – Summary of the dossier

Part 2 – Chemical, pharmaceutical and biological documentation

Part 3 – Safety and residues documentation

Part 4 – Pre-clinical and clinical documentation

Administrative documentation

Part 1 is divided into 3 sub-sections. Parts 1A, 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, manufacturing and marketing authorisations applied for or obtained elsewhere.

— Part 1 B consists of the proposed Summary of Product Characteristics (SPC), label and package insert 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 Insert

  — Part 1 B3 SPCs already approved in the Member States

— Part 1 C consists of the Expert Reports and their tabular formats. There should be separate expert reports 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 expert report to be presented separately. Target animal safety should be presented separately within the pre-clinical/clinical expert report.

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 the members of the Committee for Veterinary Medicinal Products in the evaluation of applications in the centralised procedure.

PART 1 – ADMINISTRATIVE DOCUMENTATION AND SUMMARY OF THE DOSSIER

PART 1 A ADMINISTRATIVE DATA

Part IA, the application form, is to be used for an application for a marketing authorisation of a medicinal product for veterinary use submitted to (a) the European Agency for the Evaluation of Medicinal Products under the centralised procedure or (b) a Member State (as well as Iceland, Liechtenstein and Norway) under either a national or mutual recognition procedure.

Usually a separate application form for each strength and pharmaceutical form is required.
For centralised procedures a combined application form is acceptable (information on each pharmaceutical form and strength should be provided, where appropriate).

DECLARATION and SIGNATURE

Product (invented) name:	
Strength(s):	
Pharmaceutical form:	
Active Substance(s):	
Applicant:	
Person authorised for communication*, on behalf of the Applicant:	

It is hereby confirmed that all existing data which are relevant to the quality, safety and efficacy of the veterinary medicinal product have been supplied in the dossier in Part II, Part III and Part IV where applicable.

It is hereby confirmed that fees will be paid/have been paid according to the national/Community rules**.
On behalf of the applicant:

_____
Signature(s)

_____
NAME

_____
Function

_____
Place and date (dd-mm-yy)

* *Note: please attach letter of authorisation for acting on behalf of the applicant (in Annex 5.4).*
** *Note: if fees have been paid, attach proof of payment in Annex 5.1- see information on fee payments in the Notice to Applicants, Volume 6A, chapter 7.*

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1. TYPE OF APPLICATION

Note: The following section should be completed where appropriate.
Processing number (for Competent Authority use only):

1.1 THIS APPLICATION CONCERNS:

☐ **1.1.1 A CENTRALISED PROCEDURE** (according to Council Regulation (EEC) No 2309/93)

☐ Part A ☐ Part B
Date of acceptance by CVMP: ⌊_⌋⌊_⌋⌊_⌋
(dd-mm-yy)

λ Rapporteur: _____
(Name of CVMP Member)

λ Co-rapporteur: _____
(Name of CVMP Member)

☐ **1.1.2 A MUTUAL RECOGNITION PROCEDURE** (according to Article 32 of Directive 2001/82/EC)

- Reference Member State: ……..
- Date of authorisation: (dd-mm-yy) ⌊_⌋⌊_⌋⌊_⌋
- Marketing authorisation number: .....
  (a copy of the authorisation should be provided - see section 4.2)
- Procedure number: .....

☐ **First use**

- Concerned Member State(s) (specify):

AT	BE	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HU	IS	IE	IT	LI	LT	LU
LV	MT	NL	NO	PL	PT	SE	SI	SK	UK								

☐ **Repeat Use** (please also complete section 4.2)

- Concerned Member States (specify):

AT	BE	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HU	IS	IE	IT	LI	LT	LU
LV	MT	NL	NO	PL	PT	SE	SI	SK	UK								

☐ **1.1.3 A NATIONAL PROCEDURE**

- If available, application number:

If known, is a subsequent mutual recognition procedure foreseen?

❍ No ❍ Yes

- If yes and if known, specify proposed Concerned Member State(s):

AT	BE	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HU	IS	IE	IT	LI	LT	LU
LV	MT	NL	NO	PL	PT	SE	SI	SK	UK								

1.2 IS THIS AN APPLICATION FOR A CHANGE TO YOUR EXISTING MARKETING AUTHORISATION AS REFERRED TO IN ANNEX II OF REGULATIONS (EC) NO 1084/2003 or 1085/2003 OR ANY NATIONAL LEGISLATION, WHERE APPLICABLE?

☐ **No** *(complete section 1.3. only)*

☐ **Yes** *(complete sections below and also complete section 1.3. as appropriate)*

Note: - the applicant of the present application must be the same as the marketing authorisation holder of the existing marketing authorisation
- section 1.2.1 (extension) or section 1.2.2 (not an extension) should be completed without prejudice to the provisions of Articles 12, 13.1, 14, 25 of Directive 2001/82/EC

●**For existing marketing authorisations in the Community/Member State where the application is made:**

- Name of the marketing authorisation holder: .....
- Name, strength, pharmaceutical form of the existing product: .....
- Marketing authorisation number(s): ..…….....

●**Is the present application an extension of a marketing authorisation?**

☐ **Yes** *(complete section 1.2.1)*

☐ **No** *(complete section 1.2.2)*

1.2.1	**The change to the existing marketing authorisation is considered to be an <u>extension</u> of the marketing authorisation (according to Annex II of Regulations 1084/2003 and 1085/2003). Please specify:** ☐ change or addition of a new pharmaceutical form ☐ change or addition of a new strength / potency ☐ change or addition of a new route of administration ☐ change of pharmacokinetics ☐ change of bioavailability ☐ change or addition of food-producing target animal species ☐ qualitative change in declared active substance <u>not defined as a new active substance</u> *Note: see definition in the Notice to Applicants, vol. 6A, chapter 1.* ☐ replacement by a different salt/ester, complex/derivative (same therapeutic moiety) ☐ replacement by a different isomer, mixture of isomers, of a mixture by an isolated isomer ☐ replacement of a biological substance or product of biotechnology with one of a slightly different structure; modification of the vector used to produce the antigen/source material, including a new master cell bank from a different source where the efficacy/safety characteristics are <u>not</u> significantly different ☐ other change(s), please specify: ……
1.2.2	**The change to the existing marketing authorisation is <u>not considered to be an extension</u> of the marketing authorisation. Please specify:** ☐ addition of one or more active substance(s) including antigenic components for vaccines ☐ deletion of one or more active substance(s) including antigenic components for vaccines ☐ qualitative change in declared active substance <u>defined as a new active substance</u> *Note: see definition in the Notice to Applicants, vol. 6A, chapter 1.* ☐ replacement by a different salt/ester, complex/derivative (with the same therapeutic moiety) ☐ replacement by a different isomer, different mixture of isomers, replacement of a mixture by an isolated isomer ☐ replacement of a biological substance or product of biotechnology with one of a different molecular structure ; modification of the vector used to produce the antigen/source material, including a master cell bank from a different source where the efficacy/safety characteristics are significantly different ☐ other change(s), please specify: ……

1.3 <u>THIS APPLICATION IS SUBMITTED IN ACCORDANCE WITH THE FOLLOWING ARTICLE IN DIRECTIVE 2001/82/EC</u>

Note: - section to be completed for any application, including applications referred to in section 1.2
- for further details, consult the Notice to Applicants, volume 6A, chapter 1

1.3.1 <u>A COMPLETE AND INDEPENDENT APPLICATION / STAND-ALONE APPLICATION</u>

☐ **Article 12.3 (j) - complete application (that is, complete dossier with Parts I, II, III and IV*)**

☐ New active substance

Note: - constituent of a veterinary medicinal product not yet authorised by a competent authority or by the Community (for Centralised Procedure),

☐ Known active substance

Note: - constituent of a veterinary medicinal product already authorised by a competent authority or the Community
- same or different marketing authorisation holder
- for extensions of complete applications, cross references can only be made to parts III and IV*

☐ **Article 13.1 (a)(ii), - so called "bibliographical application"**

Note: - for further details, consult the Notice to Applicants, vol.6A, chapter 1.
- for extensions of bibliographical applications, cross references can only be made to parts III and IV

1.3.2 AN ABRIDGED APPLICATION

☐ **Article 13.1 (a)(i) - so called "informed consent application"**

*Note: - application for a product **essentially similar** to an authorised product where consent has been given by the existing marketing authorisation holder to use their data in support of this application*
- complete Parts I and II should be provided, with consent to Parts III and/or IV
- the authorised product and the informed consent application can have the same or different MAH

Authorised product in the Community/Member State where the application is made:

- Product name, strength, pharmaceutical form.....
- Marketing authorisation holder: .....
- Marketing authorisation number(s): .....

☐ Attach letter of consent from the marketing authorisation holder of the authorised product (Annex 5.2)

Article 13.1 (a)(iii)

☐ **- so called "generic application"**

*Note: - application for a product **essentially similar** to a so called reference product*
- complete Parts I & II, plus data on Parts III and/or IV when applicable
- see chapter 1

Original product:

Authorised for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form:.....
- Marketing authorisation holder:.....
- First authorisation: Date:(dd-mm-yy)…….....Member State (EEA):.....
- Target species:.....

Reference medicinal product

Marketed in the Community/Member State where the application is made:

- Product name, strength, pharmaceutical form:.....
- Marketing authorisation holder:.....
- Marketing authorisation number(s):.....
- Target species:.....

Medicinal product used for bioequivalence study (where applicable):

- Product name, strength, pharmaceutical form:.....
- Marketing authorisation holder:.....
- Member State of source:.....

1.3.3 AN APPLICATION FOR A FIXED COMBINATION

☐ **Article 13.1 (b) - new product containing known active substances not used previously in combination, so called fixed combination:**

Note: - complete Parts I & II, plus data in Parts III and IV on the combination only
- for extensions of fixed combination applications, cross references can only be made to parts III and IV

1.4 MRL status (only for food producing species)

When the veterinary medicinal product is intended for use in food-producing animals, please provide the following information as available at the time of submission of the application[1].

Maximum Residue Limits (MRL) according to Council Regulation (EEC) No 2377/90 has been published in the Official Journal of the European Communities:

Substance(s)	Annex	Species	Target tissue(s)	Remarks	OJ date of publication

Application for a Maximum Residue Limit has been made to the EMEA:

Substance(s)	Date of submission	Species	Remarks

[1]*All substances contained in the product are subject to this requirement if they are pharmacologically active in the dose in which they are administered to the animal. Excipients not included in any of the Annexes of Council Regulation (EEC) No 2377/90 should also be listed and an appropriate justification given.*

2. MARKETING AUTHORISATION APPLICATION PARTICULARS

2.1. Name(s), ATCvet code and target species

2.1.1 Proposed (invented) name of the medicinal product in the Community/Member State/ Iceland/Liechtenstein/ Norway:

If different (invented) names in different Member States are proposed in a mutual recognition procedure, these should be listed in Annex 5.17.

2.1.2 Name of the active substance(s):

Note: only one name should be given for each substance in the following order of priority: INN, Ph.Eur., National Pharmacopoeia, common name, scientific name;*
** the active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant (for further details, consult the SPC Guideline)*

2.1.3 Pharmacotherapeutic group (Please use current ATCvet code):

ATCvet Code: **Group:**

Please indicate if the ATCvet Code is still pending: ☐

2.1.4 Target species:

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

2.2.1 Strength and Pharmaceutical form (use current list of standard terms - European Pharmacopoeia)

Pharmaceutical form:

Active substance(s): **Strength(s):**

2.2.2 Route(s) of administration (use current list of standard terms - European Pharmacopoeia):

2.2.3 Container, closure and any administration device(s), including description of material from which it is constructed. (Use current list of standard terms - European Pharmacopoeia.)

For each type of pack give:

2.2.3.1 Package size(s):
Note: for mutual recognition procedures, all package sizes authorised in the Reference Member State should be listed

2.2.3.3 Proposed shelf life:

2.2.3.3 Proposed shelf life (after first opening container):

2.2.3.4 Proposed shelf life (after reconstitution or dilution):

2.2.3.5 Proposed storage conditions:

2.2.3.6 Proposed storage conditions after first opening:

Attach list of mockups/samples/specimens sent with the application, as appropriate (see Notice to Applicants volume 6A, chapter 7) (Annex 5.18).

2.3 Legal status

2.3.1 Proposed administration:

- ☐ only by a veterinary surgeon
- ☐ by a veterinary surgeon or under his/her direct responsibility
- ☐ other

2.3.2 Proposed dispensing/classification:

- ☐ subject to medical prescription
- ☐ not subject to medical prescription
- ☐ subject to other controls
  specify ……

2.3.3 For veterinary products subject to medical prescription:

- ☐ veterinary product on prescription which **may** be renewed (if applicable)
- ☐ veterinary product on prescription which **may not** be renewed (if applicable)
- ☐ veterinary product on **special** prescription
- ☐ veterinary product on **restricted** prescription

(Not all the listed options are applicable in each member state. Applicants are invited to indicate which categories they are requesting, however, the member states reserve the right to apply only those

categories provided for in their national legislation.)

2.3.4 Supply for products not subject to medical prescription:

- ☐ supply through pharmacies only
- ☐ supply through non-pharmacy outlets and pharmacies (if applicable)
- ☐ supply/administration by veterinary surgeons only
- ☐ supply by pharmacies and/or veterinary surgeons for animals under his/her care
- ☐ supply through authorised distributor
- ☐ general sale

2.3.5 Promotion for products not subject to medical prescription:

- ☐ promotion to health care professionals only
- ☐ promotion to the general public and health care professionals

2.4. Marketing authorisation holder / Contact persons / Company

2.4.1 Proposed marketing authorisation holder/person legally responsible for placing the product on the market:

Name:
Address:
Country:
Telephone:
Telefax:
E-Mail:
☐ Attach proof of establishment of the applicant in the EEA (Annex 5.3)

2.4.2 Person/company authorised for communication on behalf of the applicant during the procedure in the Community/each MS:

Name of contact:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

☐ If different to 2.4.1 above,
Attach letter of authorisation (Annex 5.4)

2.4.3 Person/company authorised for communication between the marketing authorisation holder and the competent authorities in the Community/each MS after authorisation, if different from 2.4.2:

Name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

☐ If different to 2.4.1 above,
Attach letter of authorisation (Annex 5.4)

2.4.4 Qualified person in the EEA for Pharmacovigilance

Name:
Company name:
Address:
Country:
24 hour contact Telephone number:
Telefax:
E-Mail:

☐ Attach C.V. of qualified person (Annex 5.5)

2.5 Manufacturers

2.5.1 Authorised manufacturer(s) (or importer) responsible for batch release in the EEA, in accordance with Article 44 of Directive 2001/82/EC (as shown in the package insert and where applicable in the labelling or Annex II of the Commission Decision):

Name of Company:
Address:
Country:
Telephone:
Telefax:
E-Mail:

♦ Manufacturing Authorisation number:

☐ Attach copy of manufacturing authorisation (s) (Annex 5.6)

☐ Attach justification if more than one manufacturer responsible for batch release is proposed (Annex 5.7)

For Vaccines:
Details of the State laboratory or the approved laboratory designated for that purpose (OMCL) where the official batch release takes place (in accordance with Article 82 of Directive 2001/82/EC), if applicable:

Name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

2.5.1.1 Contact person in the EEA for product defects and recalls,:

Name:
Address:
Country:
24 hour contact Telephone number:
Telefax:
E-Mail:

Batch control/Testing arrangements

2.5.1.2 Site(s) in EEA or in countries with MRA/PECA in operation where batch control/testing takes place (if different from 2.5.1):

Name of the Company:
Address:
Country:
Telephone:
Telefax:
E-Mail:

Brief description of control tests carried out by the laboratory(ies) concerned:

2.5.2 Manufacturer(s) of the medicinal product and site(s) of manufacture: (Note: including manufacturing sites of any diluent/solvent presented in a separate container but forming part of the medicinal product)

Name:
Address:
Country:
Telephone:
Telefax:
E-Mail

Brief description of functions performed by manufacturer of dosage form/assembler, etc:

☐ Attach flow-chart indicating the sequence of the different sites involved in the manufacturing process (Annex 5.8)

- If the manufacturing site is in the EEA
  - Manufacturing authorisation number (under Article 44 of Directive 2001/82/EC):

☐ Attach manufacturing authorisations required under Article 44 of Directive 2001/82/EC (Annex 5.6)

- Name of qualified person: (if not mentioned in the manufacturing authorisation)

- If the manufacturing site is outside the EEA
  - ☐ Where MRA/PECA is in operation, attach equivalent of manufacturing authorisation (Annex 5.6)

  - Has the site been inspected for GMP Compliance by an EEA authority or by an authority in MRA/PECA countries?

☐ no ☐ yes

☐ If yes, please provide (Annex 5.9) for each site a statement/certificate from the competent authority which carried out the inspection, including:

- last GMP inspection date
- name of competent authority which carried out the inspection
- type of inspection (pre/post-authorisation/special/re-inspection)
- category of products and activities inspected
- outcome: GMP compliant?: ☐ no ☐ yes

2.5.3 Manufacturer(s) of the active substance(s):

Note: All manufacturing sites involved in the manufacturing process of each source of active Substance should be listed. Broker or supplier details alone are not acceptable.

Substance:
Name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

Brief description of manufacturing steps performed by manufacturing site:

- Has a Ph.Eur. Certificate of Suitability been issued for the active substance(s)?
  ☐ no ☐ yes

  If yes,
  - substance: .....
  - name of the manufacturer: .....
  - reference number: .....
  - date of last update: (dd-mm-yy).....
  ☐ Attach copy (Annex 5.10)

- Is a European Drug Master File to be used for the active substance(s)?
  ☐ no ☐ yes

  If yes,
  - substance: .....
  - name of manufacturer:.....
  - reference number for EMEA/competent authority: .....
  - date of submission: .....
  - date of last update: (dd-mm-yy).....

  ☐ Attach letter of access for Community/Member State authorities in which the application is made (see "European Drug Master File Procedure for Active Substances") (Annex 5.10)

  ☐ Attach copy of written confirmation from the manufacturer of the active substance to inform the applicant in case of modification of the manufacturing process or specifications according to Annex I of Directive 2001/82/EC (Annex 5.11)

Where an active ingredient manufacturer has been inspected by an EEA Country:

☐ *The following information should be provided in Annex 5.9 for each site:*
- *last inspection date by an EEA country*
- *name of competent authority which carried out the inspection*
- *type of inspection (pre/post-authorisation/special/re-inspection)*
- *categories of ingredient and activities inspected*
- *outcome:* ☐ *positive* ☐ *negative*

2.5.4 Contract companies used for bioavailability or bioequivalence trials

For each contract company, state where analytical tests are performed and where clinical data are collected and give:
Name:
Address:
Country:
Telephone:
Telefax:
Email:
Duty performed according to contract:
Name and country of origin of the original/reference product:

2.6 Qualitative and quantitative composition

2.6.1 Qualitative and Quantitative composition in terms of the active substance(s) and the excipient(s):

A note should be given as to which quantity the composition refers (e.g. 1 capsule).

List the active substance(s) separately from the excipient(s):

Name of active substance(s)*	Quantity	Unit	Reference/Monograph standard
1.			
2.			
3.			
etc.			

Name of excipient(s)*	Quantity	Unit	Reference/Monograph standard
1.			
2.			
3.			
etc.			

*Note: * only one name for each substance should be given in the following order of priority: INN**, Ph.Eur., National Pharmacopoeia, common name, scientific name*
*** the active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant (for further details, consult the Guideline on the SPC)*

Details of any overages should not be included in the formulation columns but stated below:

- active substance(s)	
- excipient(s)	

2.6.2 List of materials of animal origin contained or used in the manufacturing process of the medicinal product?

NONE ☐

Name	Function* AS EX R	Animal origin susceptible to TSE** *Specify species*	Other animal origin *Specify species*	Human origin	Certificate of suitability for TSE (state No.)
1.	☐ ☐ ☐	☐ species……	☐ species……	☐	☐
2.	☐ ☐ ☐	☐ species……	☐ species……	☐	☐
3.	☐ ☐ ☐	☐ species……	☐ species……	☐	☐
4.	☐ ☐ ☐	☐ species……	☐ species……	☐	☐
etc.					

* AS= active substance, EX=excipient (including starting materials used in the manufacture of the active substance/excipient), R=reagent/culture medium (including those used in the preparation of master and working cell banks)

** as defined in section 2 (scope) of the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veteirnary medicinal products

☐ If a Ph.Eur. Certificate of Suitability for TSE is available according to Resolution AP/CSP (99)4 of the Council of Europe, attach it in Annex 5.12

2.6.3 Does the medicinal product contain or consist of Genetically Modified Organisms (GMOs) within the meaning of Article 2 of Directive 1002/18/EC of the European Parliament and of the Council (formerly Council Directive 90/220/EEC)?

☐ No ☐ Yes

If yes, does the product comply with Directive 2001/18/EC?

☐ No ☐ Yes

☐ *Attach a copy of any written consent(s) of the competent authorities to the deliberate release into the environment of the GMOs for research and development purposes where provided for by Part B of the above-mentioned Directive (Annex 5.13).*

3. SCIENTIFIC ADVICE

3.1 Was formal scientific advice given by the CVMP for this medicinal product?

☐ No ☐ Yes

If yes,

Date: (dd-mm-yy)
Reference of the letter from the CVMP/EMEA:
☐ Attach copy of the letter (Annex 5.14)

3.2 Was there a scientific recommendation given by Member State(s) for this medicinal product?

☐ No ☐ Yes

If yes,

Member State(s):
Date(s): (dd-mm-yy)

4. OTHER MARKETING AUTHORISATION APPLICATIONS

4.1 FOR NATIONAL APPLICATIONS ONLY, PLEASE COMPLETE THE FOLLOWING IN ACCORDANCE WITH ART. 12.3 (M) OF DIRECTIVE 2001/82/EC:

4.1.1 Is there another Member State(s) where an application for the same* product is pending?

☐ yes ☐ no
If yes, section 4.2. must be completed

4.1.2 Is there another Member State(s) where an authorisation is granted for the same*product?

☐ yes ☐ no
If yes, section 4.2 must be completed and copy of authorisation provided

Are there any differences which have therapeutic implications between this application and the applications/authorisations for the same product in other Member States (for national applications, Articles 21 or 22 of Directive 2001/82/EC may apply).

☐ yes ☐ no
If yes, please elaborate:

4.1.3 Is there another Member State(s) where an authorisation was refused/suspended/ revoked by competent authorities for the same* product?

☐ yes ☐ no

If yes, section 4.2 must be completed

**Note: "same product" means from applicants belonging to the same mother company or group of companies or which are "licensees". (Same qualitative and quantitative composition in active substance(s) and having the same pharmaceutical form.*

4.2 Marketing authorisation applications for the <u>same</u> product in the EEA (i.e. from applicants belonging to the same mother company or group of companies OR which are "licensees". (Same qualitative and quantitative composition in active substance(s) and having the same pharmaceutical form. The same product would have the same dossier) *Note: refer to Commission Communication 98/C229/03.*

☐ <u>Authorised</u>
country:
date of authorisation: (dd-mm-yy)
invented name:
authorisation number:

☐ Attach marketing authorisation (Annex 5.15)

☐ <u>Pending</u>
country:
date of submission: (dd-mm-yy)

☐ <u>Refused</u>
country:
date of refusal: (dd-mm-yy)

☐ <u>Withdrawn (by applicant before authorisation)</u>
country:
date of withdrawal: (dd-mm-yy)
invented name:
reason for withdrawal:

☐ <u>Withdrawn (by applicant after authorisation)</u>
country:
date of withdrawal: (dd-mm-yy)
authorisation number:
reason for withdrawal:
invented name:

☐ <u>Suspended/revoked (by competent authority)</u>
country:
date of suspension: (dd-mm-yy)
reason for suspension/withdrawal:
invented name:

4.3 <u>For multiple applications of the same medicinal product:</u>

Multiple application for
Name of the other product(s):
Date of application(s): (dd-mm-yy)
Applicant(s):

☐ Attach copy of correspondence with the European Commission, for centralised procedures only (Annex 5.16)

4.4 Marketing authorisation applications for the <u>same</u> product outside the EEA (i.e. from applicants belonging to the same mother company or group of companies OR which are "licensees". (Same qualitative and quantitative composition in active substance(s) and having the same

pharmaceutical form.) *Note: refer to Commission Communication 98/C229/03*

☐ Authorised
country:
date of authorisation: (dd-mm-yy)
invented name:

☐ Pending
country:
date of submission: (dd-mm-yy)

☐ Refused
country:
date of refusal: (dd-mm-yy)

☐ Withdrawn (by applicant before authorisation)
country:
date of withdrawal: (dd-mm-yy)
invented name:
reason for withdrawal:

☐ Withdrawn (by applicant after authorisation)
country:
date of withdrawal: (dd-mm-yy)
authorisation number:
reason for withdrawal:
invented name:

☐ Suspended/revoked (by competent authority)
country:
date of suspension: (dd-mm-yy)
reason for suspension/revocation:
invented name:

5. APPENDED DOCUMENTS (WHERE APPROPRIATE)

☐ **5.1** Proof of payment.

☐ **5.2** Informed consent letter of marketing authorisation holder of authorised veterinary medicinal product.

☐ **5.3** Proof of establishment of the applicant in the EEA.

☐ **5.4** Letter of authorisation for communication on behalf of the applicant/MAH.

☐ **5.5** Curriculum Vitae of the Qualified Person for Pharmacovigilance.

☐ **5.6** Manufacturing Authorisation required under Article 44 of Directive 2001/82/EC (or equivalent outside of the EEA where MRA/PECA is in operation).

☐ **5.7** Justification for more than one manufacturer responsible for batch release in the EEA.

☐	**5.8** Flow-chart indicating the different sites involved in the manufacturing process of the medicinal product (including sites involved in sampling and testing for batch release of products manufactured in third countries).
☐	**5.9** Statement/certificate from the Competent Authority which carried out the inspection of the manufacturing site(s).
☐	**5.10** Letter(s) of access to Drug Master File(s) or copy of Ph.Eur. Certificate(s) of Suitability.
☐	**5.11** Copy of written confirmation from the manufacturer of the active substance to inform the applicant in case of modification of the manufacturing process or specifications according to Annex I of Directive 2001/82/EC.
☐	**5.12** Copy of Ph.Eur. Certificate(s) of Suitability for TSE.
☐	**5.13** Written consent(s) of the Competent Authorities regarding GMO release in the environment.
☐	**5.14** Scientific Advice given by CVMP.
☐	**5.15** Marketing Authorisation(s) required under Directive 2001/82/EC Article 12 (k) – (m) in the EEA and the equivalent in third countries on request(a photocopy of the pages which give the marketing authorisation number, the date of authorisation and the page which has been signed by the authorizing competent authority will suffice).
☐	**5.16** Correspondence with European Commission regarding multiple applications.
☐	**5.17** List of proposed invented names and marketing authorisation holders in the concerned member states.
☐	**5.18** List of Mock-ups or Samples/specimens sent with the application, as appropriate (see Notice to applicants, volume 6A, chapter 7).

PART 1 B SUMMARY OF PRODUCT CHARACTERISTICS, LABEL AND PACKAGE INSERT

PART 1 B1 – SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

See Guideline SPC Pharmaceuticals in volume 6C.

PART 1 B2 – PROPOSAL FOR PACKAGING, LABELLING AND PACKAGE INSERT

The labelling and package insert of the veterinary medicinal product, forms part of the authorisation of the product and must therefore be approved by the competent authorities. The text of the labelling or package insert must be in compliance with the SPC.

As provided in Article 12(3)(k) of Directive 2001/82/EC, an application for a marketing authorisation must include one or more specimens or mock-ups of the outer packaging and of the immediate packaging of the medicinal product, together with the draft package insert. A **mock-up** is a flat artwork design in full colour, presented so that, (following cutting and folding, where necessary), it provides a full size replica of both the outer and immediate packaging so that the three dimensional presentation of the label text is clear. The text to include in those specimens must be provided in each of the eleven languages at the time of the submission of the application.

PART 1 B3 – SPCS APPROVED IN MEMBER STATES

The approved SPCs should be provided in the national original language(s). Translations should be provided if considered appropriate.

PART 1 C EXPERT REPORTS

1. GENERAL

It is important to emphasise that well prepared expert reports 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 expert reports, which should be written in accordance with the guidance on the preparation of expert reports given below.

Authors of expert reports must be chosen on the basis of their relevant 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 expert report 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

— 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 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 expert reports must include a critical discussion of the properties of the product as demonstrated by the contents of the dossier. 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 expert reports must not be a repetition of other parts of the dossier, although important data will need to be summarised in the expert report in some form. More detailed guidance on the preferred form for summary data in expert reports is provided below under the headings of “Quality”, “Safety” and “Efficacy”. Both expert reports and summaries 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 expert reports 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 SPC, taking into account the submitted data and the SPC guideline.

For applications submitted through the decentralised procedure, the expert reports 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**.

2. EXPERT REPORTS FOR PARTICULAR TYPES OF APPLICATIONS

Informed consent from the marketing authorisation holder

For applications based upon Article 13(1)(a)(i) of Directive 2001/82/EC, the Experts’ Reports of the original marketing authorisation holder may be used and therefore need not be re-submitted.

Bibliographical applications

For applications based upon Article 13(1)(a)(ii) of Directive 2001/82/EC, the Experts’ Reports should particularly focus on the following elements:

- the grounds for using published references and the relevance of the references selected;
- an update of published literature relevant to the substance and the present application. The expert may annotate review articles published in “peer review” journals, which may be acceptable in this respect;

— a summary of impurities present in batches of the active substance(s) (and, where relevant, decomposition products arising during storage) as proposed for use in the product to be marketed;

— the issue of bioavailability, and bioequivalence where appropriate, related to the proposed formula for marketing should be addressed, taking into account the relevant pharmacokinetic parameters of the formulation used in the literature;

— comparison of pharmacokinetic parameters (Cmax, Tmax, AUC etc.) of the formulations used in the literature and the formulation proposed for marketing;

— an evaluation of the results of additional studies to provide for missing data in the file. These data should be discussed in the perspective of what is known from published literature.

— every claim in the Summary of Product Characteristics (SPC) not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the Expert Reports and substantiated by published literature and/or additional studies.

Product essentially similar to a product authorised for 6 or 10 years

For applications based upon Article 13(1)(a)(iii) of Directive 2001/82/EC, Expert Reports should particularly focus on the following elements:

— the grounds for claiming essential similarity;

— an evaluation of the bioequivalence studies or a justification why studies were not performed with respect to the note for guidance on “Conduct of bioequivalence studies in animals”;

— a summary of impurities present in batches of the active substance(s) (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed;

— every claim in the Summary of Product Characteristics (SPC) not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the Expert Report and substantiated by published literature and/or additional studies;

Changes to a marketing authorisation leading to a extension application

For applications based upon Annex II of Regulations (EC) No 1084/2003 and 1085/2003 variations, an application for a new marketing authorisation must be made.

The Expert Report 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 substance and the present application. The expert 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 Expert Report and substantiated by published literature and/or additional studies.

3. PRESENTATION OF THE EXPERT REPORTS

Experience has shown that many applications, particularly for new active substances, have included a written summary as well as the tabulations to the Expert Reports.

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

It is important to avoid duplication, repetition between the Expert Report 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.

3.1 QUALITY (PHARMACEUTICAL) EXPERT REPORT

For the expert report on the physico-chemical, biological and microbiological documentation of the dossier, the tabular formats (Q1 to Q22) are considered to fulfil the function of a written summary. In the case of medicinal products derived from biotechnology including those, which contain or consist of genetically modified organisms a written summary of not more than 30 pages should be compiled, see further guidance below.

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

INTRODUCTION AND OVERWIEV

The pharmaceutical information should be presented in the following sequence:

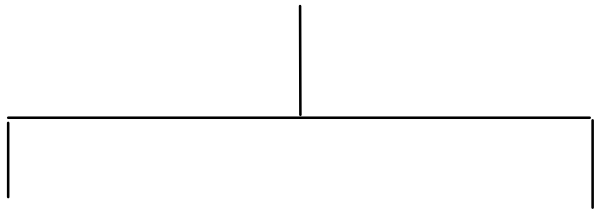
— Product profile

— Expert report

1. Composition
2. Method of preparation
3. Control of starting materials
   a) Active substance(s)
   b) Excipients
   c) Packaging material (immediate packaging)
   d) Specific measures concerning materials of animal origin with respect to TSEs
4. Control tests on intermediate products
5. Control tests on the finished product
6. Stability
   a) Stability tests on active substance(s)
   b) Stability tests on the finished product
7. Other information
8. Conclusions
9. Reference list
10. Information on the pharmaceutical expert including *Curriculum vitae* and declaration of expert, professional relationship to the applicant

Appendices to the expert report (where appropriate)

1. Tabular formats
2. Written summary



* 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).

GENERAL ASPECTS

The quality expert report should consist of a critical evaluation of the methodology, results and conclusions.

Report formats that may be used by the pharmaceutical expert 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.

“Drug Master Files”

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 Master File to ensure that all relevant information required is supplied as part of the Chemical, Pharmaceutical and Biological Documentation (Part 2) and in the Pharmaceutical Expert Report on that documentation (Part 1 C).

Confidential data on the manufacture of the active substance(s) may be submitted in separate confidential documentation. However where it is supplied separately, a separate Expert Report 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 Expert Report, 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:

1. 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).

2. Development pharmaceutics

   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.

3. 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 safety and preclinical 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 expert report 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.

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 (e.g. that a non-standard sterilisation condition provides an acceptable level of assurance of product sterility).

6. Control of pharmacopoeial active substance(s)

A discussion as to 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 Expert Report, levels found in typical batches, and the proposed test limits.

7. 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 toxico-pharmacological Expert Report 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 species and population (e.g. juvenile or adult), 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 summarised. In the case of vegetable active substances the possibility of accumulation of pesticides or diminution of micro-organisms in the vegetable active substance and potential residues of fumigants should be discussed with the levels found in typical batches and proposed test limits.

8. 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 Expert Report.

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. Specific measures concerning materials of animal origin with respect to TSEs.

The risk assessment for these materials should follow the guidance given the current Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via

human and veterinary medicinal products, with cross-reference to European Pharmacopoeia Certificates of Suitability included in the dossier, if relevant.

11. 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.

12. 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.

13. 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 toxico-pharmacological Expert Report.

14. 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.

15. 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.

16. 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”.

17. Information on the qualifications and experience of the pharmaceutical expert

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

Tabular formats for the pharmaceutical expert report

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

GUIDANCE ON THE USE OF THESE TABULAR FORMATS IS GIVEN ON PAGE 29.

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 Expert Report
Format Q1 - Composition

<table>
<tr><td>Name of Company:

Name of Finished Medicinal Product:

Name of Active substance(s)</td><td>Tabular format referring to Part 2 A of the Dossier</td><td>(For National Authority Use Only)</td></tr>
<tr><td colspan="3">PART 2 A: COMPOSITION</td></tr>
<tr><td colspan="2">Product Description: Volume Page(s)</td><td>(For National AuthorityUse Only)
COMMENTS</td></tr>
<tr><td colspan="2"></td><td rowspan="8"></td></tr>
<tr><td colspan="2">Complete Composition: Volume Page(s)</td></tr>
<tr><td colspan="2">Active substance(s) Unit and/or Percentage Formula

Excipients</td></tr>
<tr><td colspan="2">Container (brief description): Volume Page(s)</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td colspan="2">Clinical trial formulae: Volume Page(s)</td></tr>
<tr><td colspan="2">Active substance(s) Unit and/or Percentage Formula

Excipients</td></tr>
</table>

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 summarised. 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 Expert Report
Format Q2 – 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)
PART 2 A: DOSAGE FORM – DEVELOPMENT PHARMACEUTICS		
Product Development Studies Summary: Volume Page(s)		(For National Authority Use Only) COMMENTS
Explanation of choice of the composition		
Explanation of optimisation of concentrations of the additives in the composition:		
Summary of studies on compatibility data with other products (if necessary): Volume Page(s)		

Pharmaceutical Expert Report
Format Q3 – Dosage form - Development pharmaceutics

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)
PART 2 A: DOSAGE FORM – DEVELOPMENT PHARMACEUTICS		
Summary of studies on compatibility with the container/closure: Volume Page(s)		(For National Authority Use Only) COMMENTS
Summary of *in vivo* bioavailability/bioequivalence studies: Volume Page(s)		
In vitro dissolution data on products used in the *in vivo* 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 summarised.

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

Pharmaceutical Expert Report
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)
PART 2 B: METHOD OF PREPARATION		
Manufacturing formula: Volume Page(s)		(For National Authority Use Only) COMMENTS
Batch size: Formula:		
Manufacturing process (including in process control and assembly) Volume Page(s)		

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 summarised.

Pharmaceutical Expert Report
Format Q5 – Method of preparation - Process validation

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)
PART 2 B: METHOD OF PREPARATION – PROCESS VALIDATION		
Summary of experimental studies: Volume Page(s)		(For National Authority Use Only) COMMENTS

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 summarised. 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 summarised. 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 summarised (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 summarised.

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 summarised.

Pharmaceutical Expert Report
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)
PART 2 C: CONTROL OF STARTING MATERIALS – ACTIVE SUBSTANCE(S): Specifications and active tests		
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 Expert Report
Format Q7 – Control of starting materials - Active substance(s): Nomenclature and description

<table>
<tr><td>Name of Company:

Name of Finished Medicinal Product:

Name of Active substance(s)</td><td>Tabular format referring to Part 2 C of the Dossier</td><td>(For National Authority Use Only)</td></tr>
<tr><td colspan="3">PART 2 C: CONTROL OF STARTING MATERIALS – ACTIVE SUBSTANCE(S):
Nomenclature and description</td></tr>
<tr><td colspan="2">Structural Relationship to Other Known Drugs</td><td>(For National Authority Use Only) COMMENTS</td></tr>
<tr><td colspan="2"></td><td rowspan="11"></td></tr>
<tr><td colspan="2">1. Nomenclature: Volume Page(s)</td></tr>
<tr><td colspan="2">INN:

Chemical name:

Other name:

Laboratory code:

National approved name:

For starting materials of vegetable origin:

Botanical name and authority:

Definition of preparation of vegetable origin:</td></tr>
<tr><td colspan="2">2. Description: Volume Page(s)</td></tr>
<tr><td colspan="2">Physical form:</td></tr>
<tr><td colspan="2">Structural formula (include conformation if necessary):</td></tr>
<tr><td>Molecular formula:</td><td>Relative Molecular mass:</td></tr>
<tr><td colspan="2">Chirality:</td></tr>
</table>

Pharmaceutical Expert Report
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)
PART 2 C: CONTROL OF STARTING MATERIALS – ACTIVE SUBSTANCE(S): Manufacture		
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 Expert Report

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)
PART 2 C: CONTROL OF STARTING MATERIALS – ACTIVE SUBSTANCE(S): SCIENTIFIC DATA (QC during manufacture): Volume		
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 Expert Report

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 Expert Report

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)
PART 2 C: CONTROL OF STARTING MATERIALS: ACTIVE SUBSTANCE(S): (ANALYTICAL DEVELOPMENT & VALIDATION):		
Summary of Analytical Development and Validation Studies Volume Page		(For National Authority Use Only) COMMENTS

Pharmaceutical Expert Report

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

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) – (Impurities): Volume	
Potential impurities arising from the route of synthesis: Volume Page(s)	Test procedures and their limits of detection or limits of quantitation:
Potential impurities arising during the production and purification: Volume Page(s)	Test procedures and their limits of detection or limits of quantiitation:
Potential impurities/contaminants in substances of vegetable origin (e.g. micro-organisms, pesticides, fumigants, toxic metals): Volume Page	Test procedures and their limits of detection or limits of quantitation:
Impurities and structural deviants actually found (with indication of amounts): Volume Page(s)	
COMMENTS - (For National Authority Use Only)	

Pharmaceutical Expert Report
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 summarised. 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 summarised. 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 summarised.

Pharmaceutical Expert Report

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

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. EXCIPIENTS – Specifications and routine test:		
1. Excipients described in a pharmacopoeia: Volume Page(s)		(For National Authority Use Only) COMMENTS
2. Excipients not described in a pharmacopoeia: Volume Page(s)		
Characteristics: Identification tests: Purity tests: — Physical — Chemical — Biological/Immunological Other tests: Assay(s) and/or other Potency evaluation:		

Pharmaceutical Expert Report
Format Q15 – Control of starting materials - Excipients

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. EXCIPIENTS –		
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 summarised. Reference should be made to European Pharmacopoeia or national pharmacopoeia monographs where these exist.

Pharmaceutical Expert Report

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

<table>
<tr><td>Name of Company:

Name of Finished Medicinal Product:

Name of Active substance(s)</td><td>Tabular format referring to Part 2 C of the Dossier</td><td>(For National Authority Use Only)</td></tr>
<tr><td colspan="3">PART 2 C: CONTROL OF STARTING MATERIALS. PACKAGING MATERIAL (IMMEDIATE PACKAGING)</td></tr>
<tr><td colspan="2">Specifications and routine tests: Volume Page(s)</td><td>(For National Authority Use Only) COMMENTS</td></tr>
<tr><td colspan="2">Type of material:
Construction:
Quality specification (routine tests and summary of control methods):</td><td rowspan="6"></td></tr>
<tr><td colspan="2">Summary of development studies on packaging materials:
Volume Page(s)</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td colspan="2">Batch analysis (Analytical results): Volume Page(s)</td></tr>
<tr><td colspan="2"></td></tr>
</table>

PART 2 D – 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 (Official Journal of the European Union C286 of 12.10.2001, page 10 – 11. Formats are available at the EMEA (for centralised procedures) and similar formats may be available at the competent authorities in the Member States.

PART 2 E – CONTROL TESTS ON INTERMEDIATE PRODUCTS

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

PART 2 F – 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 pharmacopoeia methods.

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

Pharmaceutical Expert Report
Format Q17

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 INTERMEDIATE PRODUCTS: Volume Page(s)		(For National Authority Use Only) COMMENTS

Pharmaceutical Expert Report
Format Q18

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: 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 summarised.

Pharmaceutical Expert Report
Format Q19

<table>
<tr><td>Name of Company:

Name of Finished Medicinal Product:

Name of Active substance(s)</td><td>Tabular format referring to Part 2 F of the Dossier</td><td>(For National Authority Use Only)</td></tr>
<tr><td colspan="2">PART 2 F: CONTROL TESTS ON THE FINISHED PRODUCT – SCIENTIFIC DATA</td><td>(For National Authority Use Only) COMMENTS</td></tr>
<tr><td colspan="2">Summary of analytical development and validation studies:
Volume Page(s)</td><td rowspan="11"></td></tr>
<tr><td colspan="2"></td></tr>
<tr><td colspan="2">Batch Analyses: Volume Page(s)</td></tr>
<tr><td colspan="2">Batches Tested:
Batch (lot) number:
Date(s) of manufacture:
Place(s) of manufacture
Batch size:
Use of batch:</td></tr>
<tr><td colspan="2">Results of Batch Analyses: Volume Page(s)</td></tr>
<tr><td>Batch Nos:</td><td rowspan="2"></td></tr>
<tr><td>Tests:</td></tr>
<tr><td colspan="2">Reference Standard</td></tr>
<tr><td colspan="2"></td></tr>
</table>

PART 2 G – 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 summarised.

Pharmaceutical Expert Report
Format Q20

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)
PART 2 G: STABILITY TESTS ON ACTIVE SUBSTANCE(S) Volume		
Batches tested Page(s)		
Batch Nos:		
General test methodology Page(s)		
Accelerated test conditions (temperature °C, % Normal test conditions (temperature °C, %RH, light): RH, light):		
Test procedures (page(s)		
Assay techniques & validation: Determination of degradation products:		
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 summarised.

Pharmaceutical Expert Report
Format Q21

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)
PART 2 G: 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)		

c) In use

The data on the in use stability of the finished product i.e. broached container, in feed stability after reconstitution etc. should be summarised.

Pharmaceutical Expert Report
Format Q22

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)
PART 2 G: IN USE STABILITY TESTS		
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)		
COMMENTS – (For National Authority Use Only)		

PART 2 H – GENETICALLY MODIFIED ORGANISMS

Requirements for environmental risk assessment for products containing or consisting of genetically modified organisms (GMOs) for submission of applications for marketing authorisation for veterinary medicinal products.

Three separate guidance documents relating to the environmental risk assessment which must accompany applications for marketing authorisation of veterinary medicinal products which contain or consist of Genetically Modified Organisms (GMOs) are found in Annex I. The relevant discussion of the findings should be included in the expert report.

PART 2 Q – 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 radio-labelled active substance used in metabolic and/or pharmacokinetic studies should be provided.

Pharmaceutical Expert Report
Format Q23

Name of Company: Name of Finished Medicinal Product: Name of Active substance(s)	Tabular format referring to Part 2 Q of the Dossier	(For National Authority Use Only)
PART 2 Q – OTHER INFORMATION		
Summary of analytical test procedures used in metabolism and bioavailability studies, and Validation Studies Volume Page(s)		
Summary of synthesis of radiolabelled active substance used in metabolic and/or pharmacokinetic studies Volume Page(s)		
COMMENTS – (For National Authority Use Only)		

3.2 SAFETY AND RESIDUES REPORTS

When preparing the safety expert report, it should be remembered that Part III of the dossier is aimed at demonstrating the potential risks to man 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 Expert Report(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 i.e. A1, A2, according to Directive 2001/82/EC:

— General toxicity

— User safety

— Environmental risk assessment (ERA)

— Residues; consumer safety

The report 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 or entry to Annex II of Regulation (EEC) No 2377/90, 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 expert report are shown at the end of these notes on the Safety and Residues expert reports. 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 (1)(a)(ii) 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 some more detailed notes on specific sections of the report.

3.2.1. SAFETY EXPERT REPORT

General toxicity

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 expert report 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.

Mutagenicity – 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 mutagenic 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 physio-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. Any risks in case of accidental ingestion should also be considered.

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 (ERA)

For the section of the dossier on the environmental risk assessement, it may be appropriate to appoint a different expert to that used for the rest of the safety dossier. A brief critique 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 environmental risk 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.

3.2.2. RESIDUES EXPERT REPORT

Consumer Safety

The residues expert report 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 or entry into Annex II of Regulation (EEC) No 2377/90, 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 expert report may be adapted from the Safety Expert Report 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 some more detailed notes 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 summarised 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 (EEC) No 2377/90, 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.).

Tabular formats for the safety expert report

Safety Expert Report – Format S1

Name of Company: **Name of Product:** **Active Substancet(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 Expert Report – 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 Expert Report – 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 Expert Report – 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

Safety Expert Report – Format S5

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

PART 3A2: RELEVANT PHARMACOLOGICAL STUDIES	
2.2. Pharmacokinetics in Laboratory Animals	
Study Summary ñ 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:		

For National Authority Use Only

Safety Expert Report – 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 Expert Report – 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 (µg/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 (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.										

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

For National Authority Use Only

Safety Expert Report – 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 (µg/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 Expert Report – 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 Expert Report – 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

For National Authority Use Only

Safety Expert Report – Format S11

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

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 Expert Report – 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:	ees:	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 Expert Report – 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

For National Authority Use Only

Safety Expert Report – 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 Expert Report – Format S15

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

PART 3A3: TOXICOLOGICAL STUDIES	
3.2 Repeat Dse 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 Expert Report – Format S16

Name of Company: **Name of Product:** **ActiveSubstance(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:
Histopathology:
Ophthalmoscopy:
Other:

For National Authority Use Only

Safety Expert Report – Format S17

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

PART 3A3: TOXICOLOGICAL STUDIES
3.2 Repeat Dose Toxicity
Expert' Conclusions on Repeat Dose Toxicity

Ftional Authority Use Only

Safety Expert Report – 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 Expert Report – 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

Safety Expert Report – Format S20

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 - 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:	

For National Authority Use Only

Safety Expert Report – 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 Expert Report – Format S22

Name of Company: **Name of Product:** **Active Substance(s):**
PART 3A3: TOXICOLOGICAL STUDIES
3.4 Reproductive Toxicity
3.4.1 Effects on Reproduction
Expert's Conclusions on Reproduction Studies

For National Authority Use Only

Safety Expert Report – Format S23

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

PART 3A3: TOXICOLOGICAL STUDIES

3.4. Reproductive Toxicity

3.4.2. Embryotoxicity/Foetotoxicity including Teratogenicity

The following embryotoxicity/foetotoxicity 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

Safety Expert Report – Format S24

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

3.4 Reproductive Toxicity	
3.4.2. Embryotoxicity/Foetotoxicity including Teratogenicity	
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:	

For National Authority Use Only

Safety Expert Report – Format S25

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

3.4. Reproductive Toxicity	
3.4.2. Embryotoxicity/Foetotoxicity including Teratogenicity	
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 Expert Report – Format S26

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

PART 3A3: TOXICOLOGICAL STUDIES
3.4 Reproductive Toxicity
3.4.2. Embryotoxicity/Foetotoxicity including Teratogenicity
Expert's Conclusions on Embryotoxicity/Foetotoxicity

For National Authority Use Only

Safety Expert Report – Format S27

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

PART 3A3: TOXICOLOGICAL STUDIES
3.5 Mutagenicity

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 (*in vitro*)	
Gene mutations in eukaryotic cells	

Expert's Comments on Choice of Studies:

For National Authority Use Only

Safety Expert Report – Format S28

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

PART 3A3: TOXICOLOGICAL STUDIES
3.5 Mutagenicity
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 Expert Report – Format S29

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

PART 3A3: TOXICOLOGICAL STUDIES
3.5 Mutagenicity
Expert's Conclusions on Mutagenicity

For National Authority Use Only

Safety Expert Report – 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 Expert Report – Format S31

Name of Company: **Name of Product:** **Active Substance(s):**
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 Expert Report – 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 Expert Report – Format S33

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

PART 3A3: TOXICOLOGICAL STUDIES
3.6 Carcinogenicity
Expert's Conclusions on Carcinogenicity

For National Authority Use Only

Safety Expert Report – Format S34

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

PART 3A4: STUDIES OF OTHER EFFECTS
4.1 Special Studies including specific target organ toxicity (eg 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 Expert Report – Format S35

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

PART 3A4: STUDIES OF OTHER EFFECTS
4.2 Microbiological Studies (for compounds with antimicrobial activity)
The following studies have been carried out:

Expert's Comments on Choice of Studies

For National Authority Use Only

Safety Expert Report – Format S36

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

PART 3A4: STUDIES OF OTHER EFFECTS
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 Expert Report – Format S37

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

PART 3A4: STUDIES OF OTHER EFFECTS
4.4 Studies on Metabolites and Other Substances
The following studies have been carried out:

Expert's Comments on Choice of Studies

For National Authority Use Only

Safety Expert Report – Format S38

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

EXPERT'S CONCLUSIONS ON SAFETY
User Safety (Adverse Effects, Exposure, Risk Assessment and Risk Management)

For National Authority Use Only

Safety Expert Report – Format S39

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

EXPERT'S CONCLUSIONS ON SAFETY
Consumer Safety (Summary of NOELs and Derivation of ADI)

For National Authority Use Only

3.3 EFFICACY EXPERT REPORT

The Efficacy Expert Report 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 antimicrobial and antiparasitic 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. For antimicrobial veterinary medicinal products, choice of the doses used in the dose determination studies should be supported by appropriate pharmacokinetic and pharmacodynamic information (i.e. PK/PD modelling).

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 an abridged application, comment should be made on whether the requirements for essential similarity 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 insert.

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 – QUALITY DOCUMENTATION

A. PHYSICO-CHEMICAL, BIOLOGICAL AND MICROBIOLOGICAL DOCUMENTATION FOR CHEMICALLY DEFINED ACTIVE SUBSTANCE(S)

The principle of GMP and the detailed guidelines are applicable to all operations, which require the authorisation referred to in Article 44 of Directive 2001/82/EC. They are also relevant to all other large-scale pharmaceutical manufacturing processes, such as that undertaken for the preparation of products for use in clinical trials, where applicable.

All analytical test procedures described in the various sections of the Part 2 must be described in sufficient detail to enable the procedures to be repeated if necessary (e.g. by an official laboratory). All procedures need to be validated and the results of the validation studies must be provided.

When compiling Part 2 of the dossier, reference should be made to the relevant guidance on the quality of veterinary medicinal products.

PART 2 A COMPOSITION

1. COMPOSITION OF THE VETERINARY MEDICINAL PRODUCT

NAMES OF SUBSTANCES	QUANTITY AND/OR PERCENTAGE	FUNCTION	REFERENCE TO STANDARDS
Active substance(s)			
Excipient(s) (3)			

The qualitative and quantitative particulars of all the constituents of the veterinary medicinal product shall be described.

2. CONTAINER (BRIEF DESCRIPTION)

Nature of container materials; qualitative composition; method of closure; method of opening.

3. CLINICAL TRIAL FORMULA(E)

4. DEVELOPMENT PHARMACEUTICS

Explanation with regard to the choice of formulation, composition, substances and container, supported, if necessary, by data on development pharmaceutics. Any overage, with justification thereof, should be stated. Tests carried out during pharmaceutical development must be described in detail e.g. *in vitro* dissolution studies for solid pharmaceutical forms.

PART 2 B DESCRIPTION OF THE MANUFACTURING METHOD

1. MANUFACTURING FORMULA

(including details of batch size)

2. MANUFACTURING PROCESS

(including in-process control and the pharmaceutical assembly process.) A flow chart of the manufacturing process should be included.

3. VALIDATION OF THE PROCESS

Validation of the process should be carried out when a non-standard method of manufacture is used or for steps of the manufacturing process, which are critical for the product. Experimental data showing that the manufacturing process, using materials of the stated quality and the types of manufacturing equipment specified, is a suitable one and will consistently yield a product of the desired quality.

PART 2 C CONTROL OF STARTING MATERIALS

1. ACTIVE SUBSTANCE(S)

1.1 Specification and routine tests

1.1.1 Active substance(s) described in a pharmacopoeia

1.1.2 Active substance(s) not described in a pharmacopoeia

- Characteristics
- Identification tests
- Purity tests (including limits for named, total, other single, unidentified single and unidentified total impurities)
  - Physical
  - Chemical
- Other tests

1.2 Scientific Data

1.2.1 Nomenclature

- International non-proprietary name (INN)
- Chemical name
- Other name
- Laboratory code

1.2.2 Description

- Physical form
- Structural formula (including conformational data for macromolecules)
- Molecular formula
- Relative molecular mass
- Chirality

1.2.3 Manufacture

- Name(s) and address(es) of the site of manufacture
- Synthetic or manufacturing route (including flow chart for the process)
- Description of process (including in-process controls)
- Catalysts (solvents, reagents, auxiliary materials)
- Purification stages (include reprocessing criteria for purification steps, if applicable and supported by date)

1.2.4 Quality control during manufacture

- Starting materials
- Control tests on intermediate products (where appropriate)

1.2.5 Development chemistry

- Evidence of chemical structure (synthetic route, key intermediates, elemental analysis, mass spectrum, NMR (Nuclear Magnetic Resonance), IR (Infra Red), UV (Ultra Violet), other)
- Potential isomerism
- Physico-chemical characterisation (solubility, physical characteristics, polymorphism, pKa and pH values, other)
- Full characterisation of the primary reference material
- Analytical validation and comments on the choice of routine tests and standards (e.g. working standard)

1.2.6 Impurities

- Potential impurities originating from the route of synthesis
- Potential impurities arising during the production and purification
- Analytical test procedures and their limits of detection

1.2.7 Batch analysis

- Batches tested (date of manufacture, place of manufacture, batch size, and use of batches including batches used in pre-clinical and clinical testing)
- Results of tests
- Reference material (analytical results), primary and others

2. EXCIPIENT(S) ([3])

2.1 Specifications and routine tests

2.1.1 Excipient(s) described in a pharmacopoeia

2.1.2 Excipient(s) not described in a pharmacopoeia

- Characteristics
- Identification tests
- Purity tests (including limits for named, total, other single, unidentified single and unidentified total impurities)
  - Physical
  - Chemical
- Other tests
- Assay(s) and/or evaluations (where necessary)

2.2 Scientific data

- Data, where necessary, for example on excipient(s) used for the first time in a medicinal product.

3. PACKAGING MATERIAL (IMMEDIATE PACKAGING)

3.1. Specifications and routine tests

- Type of material
- Construction
- Quality specifications (routine tests) and test procedures

3.2. Scientific data

- Development studies on packaging materials
- Batch analysis, analytical results.

([3]) For the purposes of this section, excipients mean components other than the active substances.

PART 2 D 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 (Official Journal of the European Union C286 of 12.10.2001, page 10 – 11) and the *Position paper on the assessment of the risk of transmission of animal spongiform encephalopathy agents by master seed materials used in the production of veterinary* vaccines adopted by the Committee for Veterinary Medicinal Products (Official Journal of the European Union C286 of 12.10.2001, page 12 - 14).

PART 2 E CONTROL TESTS ON INTERMEDIATE PRODUCTS (IF NECESSARY)

A distinction should be made between in-process controls (Part2 B) and control tests on intermediate products.

PART 2 F CONTROL TESTS ON THE FINISHED PRODUCT

1. SPECIFICATIONS AND ROUTINE TESTS

1.1 Product specifications and tests for release at time of manufacture (general characteristics, specific standards)

1.2 Control Methods

1.2.1 Test procedures for identification and quantitative determination for the active substance(s).

They must be described in detail (including biological and microbiological methods where relevant), together with other tests which include those in the appropriate general monograph for the type of dosage form in the European Pharmacopoeia:

- Identification tests
- Quantitative determination of active substance(s)
- Purity tests
- Pharmaceutical tests (e.g. dissolution)

1 2.2 Identification and determination of excipient(s)

- identification tests for approved colouring materials
- determination of antimicrobial or chemical preservatives (with limits)

2. SCIENTIFIC DATA

2.1 Analytical validation of methods and comments on the choice of routine tests and standards (e.g. working standards)

2.2 Batch analyses

- Batches tested (date of manufacture, place of manufacture, batch size and use of batches)
- Results obtained
- Reference material (analytical results), primary and others

PART 2 G STABILITY

1. STABILITY TESTS ON ACTIVE SUBSTANCE(S)

- Batches tested
- General test methodology
  - accelerated test conditions

- normal test conditions
- Analytical test procedures
  - assay
  - determination of degradation products
- Validation of all test procedures including limits of detection
- Results of tests (including initial results)
- Conclusions

2. STABILITY TESTS ON THE FINISHED PRODUCT

- Quality specification for the proposed shelf-life
- Batches tested and packaging
- Study methods
  - real time studies
  - studies under other conditions
- Characteristics studied
  - physical characteristic,
  - microbiological characteristics
  - chemical characteristics
  - chromatographic characteristics
  - characteristics of the packaging (container/closure interaction with the product)
- Evaluation test procedures
  - description of test procedures
  - validation of test procedures
- Results of test (including initials and reference to degradation products)
- Conclusions
  - shelf-life and storage conditions
  - shelf-life after reconstitution and/or first opening of the product
- Ongoing stability studies

PART 2 H GENETICALLY MODIFIED ORGANISMS

Requirements for environmental risk assessment for products containing or consisting of genetically modified organisms (GMOs) for submission of applications for marketing authorisation for veterinary medicinal products.

Three separate guidance documents relating to the environmental risk assessment which must accompany applications for marketing authorisation of veterinary medicinal products which contain or consist of Genetically Modified Organisms (GMOs) are found in Annex I.

PART 2 Q OTHER INFORMATION

This part is intended for information not covered by any of the previous parts, e.g. the analytical tests used for the pharmaceutical development of the product, studies concerning metabolism and bioavailability, etc.

B. PHYSICO-CHEMICAL, BIOLOGICAL AND MICROBIOLOGICAL DOCUMENTATION FOR MEDICINAL PRODUCTS CONTAINING SUBSTANCES OF VEGETABLE ORIGIN

The principle of GMP and the detailed guidelines are applicable to all operations, which require the authorisation referred to in Article 44 of Directive 2001/82/EC. They are also relevant for all other large-scale pharmaceutical manufacturing processes, such as that undertaken in hospitals, for the preparation of products for use in clinical trials, and for wholesaling, where applicable.

All analytical test procedures described in the various sections of the Part 2 must be described in sufficient detail to enable the procedures to be repeated if necessary (e.g. by an official laboratory). All procedures need to be validated and the results of the validation studies must be provided.

When compiling Part 2 of the dossier, reference should be made to the relevant guidance on the quality of veterinary medicinal products.

PART 2 A COMPOSITION

1. COMPOSITION OF THE MEDICINAL PRODUCT

NAMES OF SUBSTANCES	QUANTITY AND/OR PERCENTAGE	FUNCTION	REFERENCE TO STANDARDS
Active substance(s)			
Excipient(s)[3]			

The qualitative and quantitative particulars of all the constituents of the veterinary medicinal product shall be described.

2. CONTAINER (BRIEF DESCRIPTION

Nature of container materials; qualitative composition; method of closure; method of opening.

3. CLINICAL TRIAL FORMULA(E)

4. DEVELOPMENT PHARMACEUTICS

Explanation with regard to the choice of formulation composition, substances and container, supported, if necessary, by data on development pharmaceutics. Any overage, with justification thereof should be stated. Tests carried out during pharmaceutical development must be described in detail e.g. *in vitro* dissolution studies for solid pharmaceutical forms.

PART 2 B DESCRIPTION OF THE MANUFACTURING METHOD

1. MANUFACTURING FORMULA

(including details of batch size)

2. MANUFACTURING PROCESS

(including in process control and the pharmaceutical assembly process). A flow chart of the manufacturing process should be included.

If active substance preparations of vegetable origin are the starting material, the description of their manufacturing process and their control should be given in Section II C.

(3) For the purposes of this section, excipients mean components other than the active substances.

3. VALIDATION OF THE PROCESS

Validation of the process should be carried out when a non-standard method of manufacture is used or for steps of the manufacturing process, which are critical for the product. Experimental data showing that the manufacturing process, using materials of the stated quality and the types of manufacturing equipment specified, is a suitable one and will consistently yield a product of the desired quality.

PART 2 C CONTROL OF STARTING MATERIALS

1. ACTIVE SUBSTANCE(S)

1.1. Specifications and routine tests

1.1.1 Active substance(s) described in a pharmacopoeia

1.1.2 Active substance(s) not described in a pharmacopoeia

- — Characteristics
- — Identification tests
- — Purity tests (including limits for named, total, other single, unidentified single and unidentified total impurities)
  - — Physical
  - — Chemical
  - — Potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, radioactivity, fumigants, etc.
- — Other tests
- — Assay(s) of excipients of active substances or active substance preparations of vegetable origin with known therapeutic activity
- — In the case of active substance preparations of vegetable origin, a monograph on the substance

1.2 Scientific Data

1.2.1 Nomenclature

- — International non-proprietary name (INN)
- — Chemical name
- — Other name
- — Laboratory code
- — In the case of active substance(s) of vegetable origin
  - — Scientific name of plant, with the name of the authority, variety and chemotype
  - — Parts employed of the herb
  - — Name of the preparation

1.2.2 Description

- — Physical form
- — Structural formula (including conformational data for macromolecules)
- — Molecular formula
- — Relative molecular mass
- — Chirality
- — Main excipients of active substances of vegetable origin based on recent scientific data

1.2.3 Manufacture

- — Name(s) and address(es) of the site of manufacture

- — Geographic source of active substance of vegetable origin
- — Synthetic or manufacturing route
- — Description of process
- — Solvents reagents, excipients
- — Purification stages

1.2.4 Quality control during manufacture

- — Starting materials
- — Control tests on intermediate products (where appropriate)

1.2.5 Development (for active substance(s) of vegetable origin)

1.2.5.1 Active substance of vegetable origin

- — Description of the active substance(s) of vegetable origin
  - — macroscopic
  - — microscopic
- — Composition and analytical research for excipients and physical characteristics
- — Investigation for adulterants of known toxic excipients
- — Analytical development and validation, commentary on the choice of routine tests and specifications

1.2.5.2 Active substance preparation (e.g. powder extract) of vegetable origin

- — Analytical chemical profile (qualitative and quantitative)
- — Detection of toxic excipients/adulterants
- — Analytical development and validation, commentary on the choice of routine tests and specifications.

1.2.6 Impurities

- — Potential impurities originating from the route of synthesis
- — Potential impurities arising during the production and purification
- — Methods detecting potential contamination of the active substance(s) of vegetable origin by micro organisms and products of micro-organisms, pesticides, fumigation agents, toxic metals, radioactivity etc.
- — Potential falsification and adulterants of the active substance(s) of vegetable origin.

1.2.7 Batch analysis

- — Batches tested (date of manufacture, place of manufacture, batch size, and use of batches including batches used in preclinical and clinical testing)
- — Results of tests
- — Reference material (analytical results), primary and others

2. EXCIPIENTS

2.1 Specifications and routine tests

2.1.l Excipients described in a pharmacopoeia

2.1.2 Excipients not described in a pharmacopoeia

- — Characteristics
- — Identification tests
- — Purity tests (including limits for named, total, other single, unidentified single and unidentified total impurities)
  - — physical

— chemical

— Other tests

— Assay(s) and/or evaluations (where necessary)

2.2 Scientific data

Data, where necessary, for example on excipient(s) used for the first time in a medicinal product.

3. PACKAGING MATERIAL (IMMEDIATE PACKAGING

3.1 Specifications and routine tests

— Type of material

— Construction

— Quality specifications (routine tests) and test procedures

3.2. Scientific data

— Development studies on packaging materials

— Batch analysis analytical results

PART 2 E CONTROL TESTS ON INTERMEDIATE PRODUCTS (IF NECESSARY

A distinction should be made between in-process controls (Part II B) and control tests on intermediate products.

PART 2 F CONTROL TESTS ON THE FINISHED PRODUCT

1. SPECIFICATIONS AND ROUTINE TESTS

1.1 Product specifications and tests for release at time of manufacture (general characteristics, specific standards)

1.2 Control Methods

1.2.1 Test procedures for identification and quantitative determination for the active substance(s).

They must be described in detail (including biological and microbiological methods where relevant), together with other tests which include those in the appropriate general monograph for the type of dosage form in the European Pharmacopoeia:

— Identification tests

— Quantitative determination of active substance(s); and additionally for active substances of vegetable origin and active substance preparations of vegetable origin, quantitative determination of excipients with known therapeutic activity.

— Purity tests

— Pharmaceutical tests (e.g. dissolution)

1.2.2 Identification and determination of excipient(s)

— Identification tests for approved colouring materials

— Determination of antimicrobial or chemical preservatives (with limits)

2. SCIENTIFIC DATA

2.1 Analytical validation of methods and comments on the choice of routine tests and standards (e.g. working standards)

2.2 Batch analyses

— Batches tested (date of manufacture, place of manufacture, batch size and use of batches)

— Results obtained

- Reference material (analytical results), primary and others

PART 2 G STABILITY

1. STABILITY TESTS ON ACTIVE SUBSTANCE(S)

- Batches tested
- General test methodology
  - accelerated test conditions
  - normal test conditions
- Analytical test procedures
  - assay
  - determination of degradation products
- Validation of all test procedures including limits of detection
- Results of tests (including initial results)
- Conclusions

2. STABILITY TESTS ON THE FINISHED PRODUCT

- Quality specification for the proposed shelf-life
- Batches tested and packaging
- Study methods
  - real time studies
  - under other conditions
- Characteristics studied
  - physical characteristics
  - microbiological characteristics
  - chemical characteristics
  - chromatographic characteristics of the packaging (container/closure interaction with the product)
- Evaluation test procedures
  - description of test procedures
  - validation of test procedures
- Results of test (including initials and reference to degradation products)
- Conclusions
  - shelf-life and storage conditions
  - shelf-life after reconstitution and/or first opening of the product
- Ongoing stability studies

PART 2 Q OTHER INFORMATION

This part is intended for information not covered by any of the previous parts, e.g. the analytical tests used for studies concerning metabolism and bioavailability, etc.

PART 3 – SAFETY AND RESIDUES DOCUMENTATION

Part 3 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.

When compiling Part 3 of the dossier, reference should be made to the following Notes for Guidance:

— Notice to Applicants and Note for Guidance on the Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin (*The rules governing medicinal products in the European Community*, Volume 8).

— Guideline on Environmental Impact Assessment (EIAS) for veterinary medicinal products (Phase I) and Note for Guidance: Environmental Risk Assessment for Veterinary Medicinal Products other than GMO-Containing and Immunological Products (Phase II).

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 3 A 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 environmental 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. 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 the application relates to food producing species and if the active substance(s) of the veterinary medicinal product concerned have previously been evaluated by the Community or the EMEA in accordance with Regulation (EEC) No 2377/90, and the substance(s) concerned has been included in Annexes I, II, or III of the Regulation, this should be clearly stated in an introduction to the safety documentation. Except in the case of applications submitted pursuant to points (i), (ii) or (iii) of Article 13(1)(a) of Directive 2001/82/EC, full copies of all the documents submitted to the Commission or the EMEA in accordance with Annex V of Regulation (EEC) No 2377/90 must be included in the documentation. Throughout the documentation the applicant should clearly identify those documents which were submitted to the Commission or EMEA in accordance with the 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 prior to or at the same time as the marketing authorisation application.

It should be noted that 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.

A.1 Precise identification of the product concerned by the application

Details of the Active Substance(s) (repeat all these items if there is more than one active substance)

1.1 International non-proprietary name (INN)

1.2 International Union of Pure and Applied Chemistry (IUPAC) name

1.3 Chemical Abstract Service (CAS) name

1.4 Classification:

- therapeutic
- pharmacological

1.5 Synonyms and abbreviations

1.6 Structural formula

1.7 Molecular formula

1.8 Relative molecular mass

1.9 Degree of impurity

1.10 Qualitative and quantitative composition of impurities

1.11 Description of physical properties

- appearance
- melting point
- boiling point
- vapour pressure
- pH
- solubility in water) expressed in g/l with an indication of temperature
- solubility in organic solvents) expressed in g/l with an indication of temperature
- octanol:water partition coefficient (Pow)
- density
- refractive index
- optical rotation

Details of the Product

Formulation

Indications

Posology

Particle size (if appropriate)

A.2 Pharmacological studies

Details should be given of all pharmacological studies, which are relevant to the evaluation of the safety of the product. It may therefore be necessary to include studies, which are also presented in Part IV of the documentation.

2.1 Pharmacodynamics

2.2 Pharmacokinetics

A.3 Toxicological studies

Details should be given of all toxicological studies, which are relevant to the evaluation of the safety of the product. Full justification must be given for the omission of any of the studies listed below.

3.1 Single dose toxicity

3.2 Repeated dose toxicity

3.3 Tolerance in the target species of animal

Details should be given of all studies, which are relevant to the evaluation of human safety. It may therefore be necessary to include studies, which are also presented in Part IV of the documentation.

3.4 Reproductive toxicity, including teratogenicity

3.4.1 Studies of the effects on reproduction

3.4.2 Embryotoxicity/foetotoxicity, including teratogenicity

3.5 Mutagenicity

3.6 Carcinogenicity (if necessary)

Full justification should be given for the omission of any of the studies listed above.

A.4 Studies of other effects

Details should be given of all other studies, which are relevant to the evaluation of the safety of the product.

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

4.2 Observations in humans

4.3 Microbiological studies (e.g. studies on human gut flora and organisms used in food processing)

4.3.1 Studies in humans

4.3.2 Studies in animals

4.3.3 *In vitro* studies

4.4 Studies on metabolites, impurities, other substances and formulation.

A.5 User safety

An assessment of the hazard presented by the product for users should be presented, incorporating the following aspects:

5.1 An appraisal of the inherent toxicity or other harmful effects such as flammability of the active substance or other components, including, as appropriate, studies on:

- skin irritation
- eye irritation
- skin sensitisation
- percutaneous toxicity, including *in vitro* absorption studies
- inhalation toxicity
- known adverse reactions to similar products

5.2 An appraisal of the exposure of the user, or others who may come into contact with the product, e.g. animal handlers, children, etc. in relation to the pharmaceutical form of the product and method of administration:

- route and degree of exposure, e.g. inhalation of vapours and dusts (including information on particle size analysis and dust generation during typical usage); skin contact (including

splashing and handling animals after application); ingestion (including accidental/deliberate misuse); and accidental self-injection

- frequency of use and volume used on each occasion
- identification of the end user, e.g. vet, farmer, small animal owner
- worst case calculations may be helpful in assessing the potential risk

5.3 Conclusions including risk management proposals regarding, as appropriate:

- contraindications and safety warning phrases
- handling technique
- other methods of controlling user exposure, e.g. engineering methods such as dust, vapour or gas extraction and packaging, such as appropriate pack sizes and special closures
- protective clothing
- action to be taken in the event of accidental exposure, e.g. self-injection, ingestion, etc.
- advice to doctors
- Occupational Exposure Limits (OELs) – if these have been set
- sufficient information to enable the user to do a risk assessment, if applicable.

A.6 Environmental risk assessment

6.1 Extent of exposure of the product, its active substances or relevant metabolites to the environment (Phase I assessment)

6.2 If necessary, a Phase II assessment, i.e. specific investigations of the following, as appropriate:

- fate and degradation in soil
- fate or behaviour in water and air
- effects on aquatic organisms
- effects on other non-target organisms

6.3 If necessary, appropriate instructions for risk management should be included in the SPC.

Conclusions

The applicant should present his overall conclusions on the safety file under the headings of user safety, environmental safety and consumer safety. It would be appropriate to include comment on assessments carried out by other official bodies such as JECFA (Joint FAO/WHO Expert Committee on Food Additives) and JMPR (Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues), etc. where appropriate. If the active substance has been entered into one of the annexes to Regulation (EEC) No 2377/90, reference should be made to the Annex entry and Summary Report, if published.

PART 3 B RESIDUE DOCUMENTATION

The residue documentation for a product intended for use in food-producing animal species 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 the substance(s) of the veterinary medicinal product concerned have previously been evaluated by the Community or the EMEA in accordance with Regulation (EEC) No 2377/90, and the substance(s) concerned has/have been included in Annexes I, II or III of the Regulation, this should be clearly stated in the introduction to the residue documentation. Except in the case of applications submitted pursuant to points (i), (ii) or (iii) of Article 13(1)(a) of Directive 2001/82/EC, full copies of all the documents submitted to the Commission or the EMEA in accordance with Annex V of Regulation (EEC) No 2377/90 must be included in the documentation. Throughout the documentation the applicant should clearly identify those documents which were submitted to the Commission or EMEA in accordance with the 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) 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 prior to or at the same time as marketing authorisation application. This also applies to pharmacologically active excipients.

B.1 Precise identification of the product concerned by the application

The substance concerned should be identified in accordance with Part A.1. However, the following additional information should also be provided:

1.1 Formulation used in residue studies (related to the formulation of the final product)

1.2 For radio-tracer studies, the nature and position of the label, the activity and the radio purity of the labelled substances

B.2 Residue Studies

2.1 Pharmacokinetics (absorption, distribution, biotransformation, excretion in the target species by the relevant route(s) of administration)

2.2 Depletion of residues

2.3 MRLs

2.4 Withdrawal periods (calculated, whenever possible, using the CVMP recommended statistical method).

B.3 Analytical Method(s)

3.1 Description of the method (in an internationally recognised format, e.g. ISO 78/2)

3.2 Validation of the method

3.2.1 specificity

3.2.2 accuracy, including sensitivity

3.2.3 precision

3.2.4 limit of detection

3.2.5 limit of quantitation

3.2.6 practicability and applicability under normal laboratory conditions

3.2.7 susceptibility to interference

3.2.8 storage stability (if samples not analysed immediately)

Conclusions

Separately from the expert report, the applicant should present his own conclusions on the results of the residue studies, including proposals for withdrawal periods for the product concerned

PART 4 – EFFICACY DOCUMENTATION

PRE-CLINICAL AND CLINICAL DOCUMENTATION

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.

1. PRE-CLINICAL DOCUMENTATION

A1: PHARMACODYNAMICS

All important data should be summarised and/or presented in tabular form. The mode of action and the pharmacodynamic action in relation to the therapeutic effect should be described. The optimal dose and conditions of administration should be detailed. The pharmacodynamic actions not correlated with the therapeutic effect should also be described. This is of particular relevance to products such as anthelmintics and ectoparasiticides, for which the implications of the pharmacodynamic activity as far as the host animal is concerned should be examined.

The actions on different organs or physiological functions should be discussed, and the unwanted effects evaluated as a function of dose, in addition to those, which might have been anticipated on the basis of the demonstrated pharmacodynamic properties.

The methodology and results of any dose titration studies should be summarised. Where such studies have not been undertaken, the reasons for the selection of the dosage need to be outlined. In cases where the selection of dosage is based on information derived from bibliographical references, the relevance of these references and their precise location within the main body of the dossier should be made clear.

A2: PHARMACOKINETICS

The summary should provide the basic pharmacokinetic profile and parameters, dealing with the active substance(s) and, where appropriate, active metabolites. The following pharmacokinetic characteristics should be included:

— absorption rate and extent;

— distribution, including binding with plasma proteins;

— metabolism, including the formation of active and inactive metabolites;

— excretion of the unchanged substance and/or metabolites.

Parameters relevant to the rate and route of elimination should be included, as should any features of clinical significance such as diffusion into body fluids and target tissues, accumulation, and the role of metabolites in the clinical effect. The clinical significance of systemic absorption, with respect to possible adverse effects, should be outlined.

The pharmacokinetic results [Cmax (maximum concentration in plasma), Tmax (Time to Cmax), AUC (Area Under the Curve)] of bioavailability or bioequivalence studies should be summarised and relevant data presented in tables and/or graphs. The conclusions drawn from appropriate statistical analyses should be presented, taking into account, where appropriate, and the results of dissolution rate studies.

Comment should be made on the systemic absorption of pharmaceutical forms, which are intended to have a non-systemic effect. Studies and results with blood/plasma, urine or faeces levels should be summarised. The clinical significance of systemic absorption, with respect to possible adverse effects, should be discussed.

If a pharmacodynamic and/or pharmacokinetic interaction exists between the substance and other veterinary medicinal products, or substances, or if such action is likely, this should be described. Its clinical relevance should be outlined and consideration given to any statement concerning interaction in the proposed summary of product characteristics.

If appropriate, it would be helpful for attention to be drawn to the relevant results of the clinical pharmacological studies as well as the clinical trials. If pharmacokinetic data is further supported by the information contained in bibliographical references, the relevance of these references and their precise location within the main body of the dossier should be made clear.

B: TARGET SPECIES TOLERANCE

The methodology and results of target species tolerance studies should be summarised, with particular emphasis on the numbers of animals used, the duration of the studies and the conditions under which they were conducted, and the dosage rates employed. The method of detection and assessment of any adverse reactions should be described. An assessment of the nature, seriousness and causality of any adverse reactions would be helpful, as would a brief discussion of the benefit/risk ratio. Any warning statements in the proposed summary of product characteristics regarding adverse reactions, contra-indications, interactions, and precautions for use should also be discussed.

It would be helpful if attention could be drawn to the results of any other studies, which may have been conducted, such as dose confirmation or field studies, where they support the results of tolerance studies. If the degree of tolerance is further supported by the information contained in bibliographical references, the relevance of these references and their precise location within the main body of the dossier should be made clear.

A Guideline on Evaluation of the Safety of Veterinary Medicinal Products for the Target Animals is available and may be consulted (which includes guidance on studies for local tolerance for injectable formulations).

C: RESISTANCE

A summary of the degree to which resistance to the active substance(s) has developed and the mechanisms by which it has developed should be included, together with a commentary on its speed of development and geographical distribution, and an analysis of the likely effects of such factors on the efficacy of the product. Reference should be made to any advice regarding usage of the product in order to discourage the development of resistance, which should be included in the summary of product characteristics. If there is no evidence of resistance, a brief discussion of the most likely methods by which it may develop would be helpful.

If the lack of evidence of resistance is based on a survey of the published literature, it should be made clear whether the literature was scanned for this purpose, or whether a lack of mention has been construed as an indication that it does not exist.

2. CLINICAL DOCUMENTATION

The summary of the results and critical evaluations of dose determination and dose confirmation studies and clinical trials should give a clear picture of the therapeutic efficacy and safety of the active substances.

A tabular presentation of all clinical trials and studies should be given. This should contain the principal characteristics of the trials, such as the title of the study and the country in which it took place, the design, the number of animals, the dose regimen and route of administration, the duration of treatment, the reference veterinary medicinal product, if any, criteria and results for evaluation. Information relating to controlled trials and non-controlled trials should be presented successively.

The most important and significant studies should be summarised individually. A tabular presentation would be helpful. The trials which gave unequivocal evidence of efficacy and which provided justification for the dosage regime should be emphasised.

The compilation of the narrative and tabular information should facilitate clear understanding of the protocol, with particular reference to the objectives, design, study participants characteristics, type and

duration of treatment, criteria for evaluation of efficacy and safety, and statistical evaluations. Any deviations from the protocol should be highlighted. The numbers of animals participating in the trials, the comparability of the groups, the numbers of animals which were withdrawn or dropped-out, with reasons, and the numbers of observations available for efficacy and safety analyses should be detailed. Factors of relevance, such as geographical distribution, climatic conditions, management and husbandry factors, levels of activity of different groups, and the levels of challenge experienced under field conditions should be highlighted.

The number of trials showing a positive and negative result should be included, accompanied by appropriate explanations. The results of each parameter of efficacy should be presented, with the results of statistical evaluation. The number and percentage of animals withdrawn due to lack of efficacy should be given, as also should the number of animals withdrawn for other reasons together with an explanation of the reason for their withdrawal. The clinical significance of the results should be discussed and the possibility of bias addressed. Where appropriate, the efficacy results should be presented as a function of the dose administered and the relationship between efficacy and the dosage regimen justified and defined for each indication.

Comments should be included on the quality control of trials, on the suitability of the product formulations used, and on the degree to which there was conformity with the principles of good clinical practice during the conduct of the trials.

For veterinary medicinal products intended for long term use, maintenance of long term efficacy and the establishment of long term dosage regimes should be discussed, with reference to the possibility of the development of resistance, where appropriate. For fixed combinations, the therapeutic value should be considered by comparison to each of the individual components used separately. The doses and proportions of the components should be justified, and the therapeutic advantages of such an association should be presented.

The degree of tolerance should be assessed, and any adverse reactions summarised, together with statistical evaluation, and a clinical judgement should be made on the relationship to treatment, frequency and the seriousness of the observed adverse events. A recommendation as to the conditions of use, which would reduce the impact of adverse reactions, would be helpful.

IMMUNOLOGICALS

INTRODUCTION

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.

The current section is therefore presented, as in the previous section related to pharmaceuticals, in four Parts. In Directive 2001/82/EC these Parts are referred to in Annex I as Parts 5, 6, 7, 8 and 9 but for convenience the numbering can remain the same as that for veterinary medicinal products other than immunological products described in the preceding chapters.

Part 1 – Summary of the dossier

Part 2 – Physico-chemical, biological and microbiological documentation

Part 3 – Safety documentation

Part 4 – Pre-clinical and clinical documentation.

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, manufacturing and marketing authorisations applied for or obtained elsewhere.

— Part 1 B consists of the proposed Summary of Product Characteristics (SPC), label and package insert 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 Insert

  — Part 1 B3 SPCs already approved in the Member States

— Part 1 C consists of the Expert Reports and their tabular formats. There should be separate expert reports 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 expert report to be presented separately. Target animal safety should be presented separately within the pre-clinical/clinical expert report.

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 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.

PART 1 – ADMINISTRATIVE DATA AND SUMMARY OF THE DOSSIER

PART 1 A ADMINISTRATIVE DATA

STANDARD APPLICATION FORM

Part 1 A application form (p. 7) is to be used for applications for marketing authorisation for all veterinary medicinal products submitted in Member States, for either national or mutual recognition applications, and in the European Agency for the Evaluation of Medicinal Products for centralised applications.

PART 1 B SUMMARY OF PRODUCT CHARACTERISTICS, LABEL AND PACKAGE INSERT

PART 1 B1 – SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

See Guideline SPC Immunologicals in volume 6C.

PART 1 B2 – PROPOSAL FOR PACKAGING, LABELLING AND PACKAGE INSERT

The labelling and package insert of the immunological veterinary medicinal product, forms part of the authorisation of the product and must therefore be approved by the competent authorities. The text of the labelling or package insert must be in compliance with the SPC.

As provided in Article 12(3)(k) of Directive 2001/82/EC, an application for a marketing authorisation must include one or more specimens or mock-ups of the outer packaging and of the immediate packaging of the medicinal product, together with the draft package insert. A **mock-up** is a flat artwork design in full colour, presented so that, (following cutting and folding, where necessary), it provides a full size replica of both the outer and immediate packaging so that the three dimensional presentation of the label text is clear. The text to include in those specimens must be provided in each of the eleven languages at the time of the submission of the application.

PART 1 B3 – SPCS APPROVED IN MEMBER STATES

The approved SPCs should be provided in the national language(s). Translations should be provided if considered appropriate.

PART 1 C EXPERT REPORTS

1. GENERAL

It is important to emphasise that well prepared expert reports 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 expert reports, following the guidance on the preparation of expert reports given below.

Authors of expert reports 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 expert report 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 expert reports 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 expert reports must not be a repetition of other parts of the dossier, although important data will need to be summarised in the expert report 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 expert reports.

More detailed guidance on the preferred form for summary data in expert reports is provided below under the headings of Production and control, Safety and Efficacy. Both expert reports and summaries 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 expert reports 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 SPC guidelines.

For applications submitted through the decentralised procedure, the expert reports and summary tables must cover all the data submitted in support of the application, **including any data collected after the grant of the initial authorisation.**

2. ANALYTICAL EXPERT REPORT

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 expert report 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 found in Annex I.

It is assumed, since the analytical expert has written and signed his/her expert report, 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 that 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 pharmaceutics

   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 pharmacopoeia active substance(s)

   A discussion of any deviations from pharmacopoeia monographs.

7. Control of non-pharmacopoeia 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 expert report.

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. Specific measures concerning materials of animal origin with respect to TSEs.

    The risk assessment for these materials should follow the guidance given the current Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, with cross-reference to European Pharmacopoeia Certificates of Suitability included in the dossier, if relevant.

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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”.

17. Information on the qualifications and experience of the analytical expert

    The qualifications and experience of the expert should be briefly summarised. Although only one expert may assume responsibility for the report other experts may contribute to it.

3. SAFETY EXPERT REPORT

For the safety expert report 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 expert report 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 Expert Report, 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 that 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. Fulfillment of requirements of European Pharmacopoeia Monographs, if such exist for the product.
4. The evidence for safety in these animals;
5. The safety or risks to the operator or of waste materials emanating from the use of the product;
6. 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 expert report 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.

4. EFFICACY EXPERT REPORT

For the efficacy expert report 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 expert report 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 Expert Report, 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 that 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 (e.g. route of administration, dosage regimen etc.);
3. Fulfillment of requirements of European Pharmacopoeia Monographs, if such exist for the product.
4. How far the evidence presented supports the claims made for the product.
5. The substantiation of any stated or implied claims regarding nature, strength and duration of immunity.

TECHNICAL DOCUMENTATION

PART 2 – QUALITY DOCUMENTATION – PRODUCTION AND CONTROL

(Part 6 of the Annex to Directive 2001/82/EC)

All analytical test procedures must be described in sufficient detail to enable the procedure to be repeated if necessary (e.g. by an official laboratory). All procedures need to be validated and the results of the validation studies must be provided, taking into account all relevant guidelines.

PART 2 A – QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE COMPOSITION

(Part 6A of the Annex to Directive 2001/82/EC)

1. COMPOSITION OF THE IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCT

Details on the composition of the immunological veterinary medicinal product shall be given in the following format:

Names of substances (1)	Quantity (2)	Function / dose or /ml	Reference to standards
Active Substances			
Constituents of the adjuvant			
Constituents of the excipients (3)			
Constituents of the diluent			
Constituents of the pharmaceutical form			

(1) See Part 6 A.2 of the Annex to the Directive

(2) See Part 6 A.3 of the Annex to the Directive

(3) For the purposes of this section, excipients mean substances other than the active substance and the adjuvant, blended to prepare the finished product.

2. CONTAINER

A brief description should be given of the following particulars:

a) nature of the container materials

b) qualitative composition of the container

c) method of closure and opening

d) details of sterilisation of container components

Reference to pharmacopoeial requirements should be made.

Any specifications and certificates should be given in an Annex to this Part of the application dossier.

3. DEVELOPMENT PHARMACEUTICS

An explanation should be provided with regard to the composition, components and containers, supported by scientific data on development pharmaceutics. The overage, with justification thereof, should be stated. The efficacy of any new preservative system should be demonstrated.

4. COMPOSITION OF THE BATCHES USED IN THE CLINICAL TRIALS

PART 2 B – DESCRIPTION OF THE METHOD OF PREPARATION OF THE FINISHED PRODUCT

(Part 6B of the Annex to Directive 2001/82/EC)

1. A flow chart of the method of preparation of the immunological veterinary medicinal product should be given, showing each step in the manufacturing process, from start (e.g. production of the active substance) to finish (e.g. blending of the finished product). The batch size of a typical production lot should be given.

2. A detailed description of each step in the flow chart should be given. For blending, this should include in a tabular form, the quantitative particulars of all the substances used, following the layout given in Part 2 A 1, as far as possible.

3. Results of relevant validation studies for processes applied should be given.

PART 2 C – PRODUCTION AND CONTROL OF THE STARTING MATERIALS

(Part 6 C of the Annex to the Directive 2001/82/EC)

Starting materials means all components used in the production of the immunological veterinary medicinal product.

The monographs of the European Pharmacopoeia are applicable to all substances 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.

Information in the dossier for application for marketing authorisation should be given as indicated below, according to the nature of the starting material in question.

Documentation from suppliers such as certificates of analysis should be given in an annex to this Part of the application dossier.

1. Starting materials listed in a pharmacopoeia

1.1 The title of the EP monograph or, in the absence thereof, the title and a copy of the monograph in a national pharmacopoeia. The production of the starting material must be shown to be in line with the requirements of the monograph referred to in the dossier.

1.2 Name, code, etc. identifying precisely the starting material

2. Starting materials not in a pharmacopoeia

2.1 Starting materials of biological origin ([1])([2])

2.1.1 Name, code, etc. identifying precisely the starting material

2.1.2 Description of the following particulars

a) details of the source

b) complete passage history of all seed materials (e.g. cells, viruses, bacteria)

c) preparation and description of master seed lot

d) controls and tests carried out on master seed lot

e) preparation and description of working seed lot

f) controls and tests carried out on working seed lot

g) storage conditions of master and working seed lots.

2.1.3 Function

2.1.4 Identification and characteristics

2.1.5 Processes with description of in-process controls and description of validation

a) amplification/culture

b) purification

([1]) All the items listed may not always be applicable for all products.

([2]) Include here details of media substances of biological origin and mention the substance again under 2.2 and/or 2.3, as appropriate.

c) inactivation

2.1.6 Genetic engineering - vaccines produced by means of recombinant DNA technology

a) Source materials:

— gene of interest: name, origin, isolation strategy, sequence;

— description of the starting strains(s) or cell line(s): name, origin, history, identification, characteristics, potential microbial and/or viral contaminants;

b) Preparation of the production strain or cell line:

— construction of the expression vector: name, origin, function of the replicon, promoter, enhancer and other regulator elements, genes used for selection, other open reading frames; mode of introduction into the production strain;

— relevant data on fusion and cloning;

c) Description of the production strain or cell line:

— biological properties of the various elements found in the final construct and details of the added gene(s) expressed; occurrence of the vector in the cell (integrated or extrachromosomal); copy number;

— demonstration that the construction is actually identical to that desired;

d) Constitutive or controlled expression

e) Genetic stability:

— constructional stability;

— segregational stability;

— stability up to and beyond the maximum passage level used for full-scale production. Where continuous culture is used for production, genetic stability under these conditions must be demonstrated.

2.2 Starting materials of non-biological origin

2.2.1 Name(s) of the starting material

a) trade-name

b) scientific synonyms

2.2.2 Description and function of the starting material

2.2.3 Methods of identification

2.2.4 Purity

2.2.5 Shelf life

2.2.6 Controls and tests performed on the starting materials

2.3 In-house preparation of media ([3])

2.3.1 Starting materials for the preparation of in-house medium

2.3.2 Quantitative composition of the medium

2.3.3 Method of preparation, including sterilisation procedure and its validation

2.3.4 Controls and tests carried out on in house media

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

(Part 6D of the Annex to the Directive 2001/82/EC)

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*

([3]) Media purchased by the manufacturer should be covered under item 2.2.

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 (Official Journal of the European Union C286 of 12.10.2001, page 10 – 11) and the *Position paper on the assessment of the risk of transmission of animal spongiform encephalopathy agents by master seed materials used in the production of veterinary* vaccines adopted by the Committee for Veterinary Medicinal Products (Official Journal of the European Union C286 of 12.10.2001, page 12 - 14).

PART 2 E – CONTROL TESTS DURING PRODUCTION

(Part 6E of the Annex to the Directive 2001/82/EC)

Whenever a coding system is used for the purposes of GMP, the same code should be used throughout this section.

Information should be presented as follows:

1. Flow chart of the production process with indication and identification code of the stages at which in-process control tests are carried out.

2. For each control stage, the following information must be given:

2.1 Title and code of the test(s) performed

2.2 Timing/frequency of the testing

2.3 Function of the test

2.4 Brief description of the test

(The detailed description of each test should be given in an annex to this Part of the application dossier, together with the details and results of the validation studies, which have been undertaken.)

2.5 Limits of acceptance of results

3. Results of the tests carried out on 3 consecutive production runs of the product in question should be given.

PART 2 F – CONTROL TESTS OF THE FINISHED PRODUCT

(Part 6 F of the Annex to the Directive 2001/82/EC)

1. For each test on the finished product, the following information should be given:

1.1 Title and code of the test(s) performed

1.2 Timing/frequency of the testing

1.3 Function of the test

1.4 Brief description of the test, including details of the samples used for the test
(The detailed description of each test should be given in an annex to this part of the application dossier, together with the details and results of the validation studies, which have been undertaken.)

1.5 Limits of acceptance of results.

2. Results of these tests should be given for three consecutive production runs of the product in question and summarised in the format which would be used for presentation of batch results to competent authorities.

PART 2 G – STABILITY

(Part 6 G of the Annex to the Directive 2001/82/EC)

1. Stability of the finished product

1.1 A summary table should be presented, showing the storage conditions and corresponding proposed shelf-life

1.2 For each parameter studied, the following information must be given for at least 3 batches

1.2.1 Tests carried out

1.2.2 Brief description of each test (The detailed description of each test should be given in an annex to this part of the application dossier)

1.2.3 Table of results with batch number, date of manufacture, dates of testing. Justification for the proposed shelf life should be given

2. Stability of the reconstituted product

2.1 A summary table should be presented, showing the storage conditions and corresponding proposed shelf-life

2.2 For each parameter studied, the following information must be given for at least 3 batches

2.2.1 Tests carried out

2.2.2 Brief description of each test

(The detailed description of each test should be given in an annex to this part of the application dossier)

2.2.3 Table of results with batch number, date of manufacture, dates of testing

2.3 Justification for the proposed shelf life should be given

PART 2 H – GENETICALLY MODIFIED ORGANISMS

Requirements for environmental risk assessment for products containing or consisting of genetically modified organisms (GMOs) for submission of applications for marketing authorisation for veterinary medicinal products.

Three separate guidance documents relating to the environmental risk assessment which must accompany applications for marketing authorisation of veterinary medicinal products which contain or consist of Genetically Modified Organisms (GMOs) are found in Annex I.

PART 3 – SAFETY DOCUMENTATION

(Parts 7 and 9 of Annex I to Directive 2001/82EC)

1. Introduction

As in any scientific work, the dossier of safety testing should include an introduction defining the subject and indicate the tests, which have been carried out. Omission of tests listed in Part 7 of the Directive should be mentioned and justified.

Certificates of compliance with Good Laboratory Practice (GLP) should be given in an annex to this part of the application dossier.

2. Laboratory tests and field studies

Details relating to each study should be given in the following order under the following headings:

2.1 Title of the test, with reference number

2.2 Introduction including a statement of the aims of the test or study

2.3 Reference to relevant EP monograph

2.4 Name of persons and test bodies involved in the test or study

2.5 Dates of start and end of the test or study

2.6 Summary

2.7 Material and methods

2.8 Results

2.9 Discussion

2.10 Conclusions

PART 4 – EFFICACY DOCUMENTATION

(Parts 8 and 9 of Annex I to Directive 2001/82EC)

1. Introduction

   As in any scientific work the dossier of efficacy testing should include an introduction defining the subject and indicate the studies and trials, which have been carried out. Omission of tests listed in Part 8 of the Directive and/or indicated in any appropriate European Pharmacopoeia monograph, should be mentioned and justified.

2. Laboratory and field trials

   For each study or trial undertaken, details should be given in the following order, under the following headings:

2.1 Title of the study or trial, with reference number

2.2 Introduction including a statement of the aims of the study or trial

2.3 Reference to relevant EP monograph

2.4 Name of persons and test bodies involved in the study

2.5 Dates of start and end of the study

2.6 Summary

2.7 Material and methods

2.8 Results

2.9 Discussion

2.10 Conclusion

BIBLIOGRAPHICAL REFERENCES

A list and copies of all bibliographical references cited in support of the application should be given.

LIST OF ABBREVIATIONS

AIM	Active Ingredient Manufacturer
CAR	Committee Assessment Report
CMS	Concerned Member State
CPMP	Committee of Pharmaceutical Medicinal Products
CRMP	Community Register of Medicinal Products
CRVMP	Community Register of Veterinary Medicinal Products
CVMP	Committee of Veterinary Medicinal Products
DMF	Drug Master File
EEA	European Economic Area
EMEA	European Agency for the Evaluation of Medicinal Products
EPAR	European Public Assessment Report
EVAF	European Variation Application Form
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
INN	International non-proprietary Name
M.A	Marketing Authorisation
MAH	Marketing Authorisation Holder
MR	Mutual Recognition
MRA	Mutual Recognition Agreement
MRL	Maximum Residue Limits
NA	New application
NfG	Note for Guidance
NTA	Notice to Applicants
OJ	Official Journal
PSUR	Periodic Safety Update Report
RMS	Reference Member State
SMF	Site Master File
SOP	Standard Operating Procedure
SPC	Summary of the Product Characteristics
V	Variation
VAR	Variation Assessment Report
VMRF	Veterinary Mutual Recognition Facilitation Group

ANNEX I – GUIDANCE ON ENVIRONMENTAL RISK ASSESSMENT FOR GMO:S

VETERINARY MEDICINAL PRODUCTS CONSISTING OF OR CONTAINING GENETICALLY MODIFIED ORGANISMS

This Chapter contains three separate guidance documents relating to the environmental risk assessment which must accompany applications for marketing authorisation of veterinary medicinal products which consist of or contain Genetically Modified Organisms (GMOs)[1],[2].

These guidelines should be read in conjunction with the current versions of the EMEA Standard Operating Procedures EMEA/CVMP/036/97 – REVISION and EMEA/CVMP/037/97 – REVISION.

Contents

[1] OJ L 106, 17.4.2001, p. 1. Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.

[2] This guidance does not apply to products which are made using Genetically Modified Organisms but which, by virtue of the manufacturing method and with appropriate validation, do not contain or consist of GMOs

A. GUIDELINE ON THE PRESENTATION OF PARTICULARS CONCERNING THE ENVIRONMENTAL RISK ASSESSMENT FOR VETERINARY MEDICINAL PRODUCTS WHICH CONTAIN, OR CONSIST OF, GENETICALLY MODIFIED ORGANISMS.

1. INTRODUCTION

This text provides detailed guidance on the form in which the particulars relevant to the environmental risk assessment are to be presented by the Applicant as part of his/her application for authorisation to market a medicinal product for veterinary use which contains, or consists of, a genetically modified organism (GMO). It is important to distinguish carefully between products which contain substances simply derived from Genetically Modified Organisms, and those products which contain, or consist of, such organisms. While advanced methods of genetic modification such as recombinant DNA technology have been applied in several instances to micro-organisms for the purpose of producing drug substances from them, micro-organisms which have been genetically modified by such means and retain a capacity for replication, have only rarely themselves been developed for administration to animals for therapeutic or diagnostic purposes.

Directive 2001/18/EC of the European Parliament and of the Council[3] on the deliberate release into the environment of Genetically Modified Organisms requires that Applicants wishing to place on the market a product which contains, or consists of, a Genetically Modified Organism (GMOs) shall submit a notification for evaluation to an appropriate Competent Authority designated for carrying out the Directive's requirements. These provisions do not, however, apply to products containing, or consisting of GMOs covered by other Community legislation, which provides for a specific environmental risk assessment similar to that laid down in the Directive. Where a notification is required by the Directive, it must include at least the following:

- specified information relating to the product and the release (Annex IIA of the Directive), including any relevant data arising from previous releases involving research and development, and an environmental risk assessment, and details of any proposed conditions for placing on the market of the product (Annex III of the Directive), including conditions related to use, handling, labeling and packaging where relevant.

- The notification is evaluated according to defined procedures. Deliberate release may proceed only if the Applicant receives a formal consent, and is subject to any conditions specified in the consent.

However, where it is the case that the GMO constitutes, or more likely is contained in, a medicinal product, then, following from provisions appearing in Article 28 of Council Regulation (EEC) No.2309/93 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products:

- the above particulars shall accompany the application for authorisation to market a medicinal product;
- these particulars shall include in addition a copy of any previously obtained written consent or consents for deliberate release for research and development purposes;
- as these requirements provide for a specific environmental risk assessment similar to that laid down in Directive 2001/18/EC , the provisions of the Directive relating to placing a medicinal product on the market no longer apply; (it should be noted that the provisions of the Directive relating to research and development or any purpose other than placing a medicinal product on the market continue to apply where relevant) and;
- during the process of evaluating applications for marketing authorisations for such products, necessary consultations will be held by the Rapporteur with those bodies set up by the Community or the Member States in accordance with Directive 2001/18/EC.

2. DEFINITIONS

The definitions, which appear in European Community law, apply. The following extracts from these are intended for the purpose of introduction only.

Medicinal Product: any substance or combination of substances presented for preventing or treating disease in human beings or animals.

Immunological Veterinary Medicinal Product: a veterinary medicinal product administered to animals in order to produce active or passive immunity, or to diagnose the state of immunity.

Organism: any biological entity capable of replication: or of transferring genetic material.

Genetically Modified Organism (GMO): an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

Deliberate Release: any intentional introduction into the environment of a GMO or a combination of GMOs without provision for containment such as physical barriers or a combination of physical barriers together with chemical and/or biological barriers used to limit their contact with the general population and the environment.

Environmental Risk Assessment: the evaluation of the risk to human health and the environment (which includes plants and animals) connected with the release of GMOs or products containing GMOs.

3. GENERAL CONSIDERATIONS

3.1 It is essential that the approach to the environmental risk assessment presented by the Applicant is similar to that laid down in Directive 2001/18/EC, including the relevant parts of Annexes IIA and III of the Directive. Headings in Annex IIA of the Directive have been omitted in this Note for Guidance in the cases in which it is considered that they are normally not applicable to medicinal products for veterinary use or to their placing on the market.

3.2 The particulars presented in accordance with this Note for Guidance will be in addition to the documentation already required in support of the claimed quality, safety and efficacy of the product. In the case of overlapping requirements the information should be repeated in full as necessary, though the data provided will in many cases be identical to data appearing in the remainder of the dossier. The Applicant will obviously need to take care to ensure consistency in the presentation of data. The various requirements affecting tests, trials, documentation etc, stated in the *Rules Governing Medicinal Products in The European Union,* as with the rest of the dossier, apply where relevant.

3.3 The particulars submitted in accordance with this Note for Guidance should form part of the dossier submitted in support of the application for marketing authorisation, and should therefore be bound, paginated and indexed as such.

3.4 Binding, pagination and indexation should be logical and thorough as stated elsewhere in the Notice to Applicants.

3.5 The particulars outlined in this Note for Guidance should be presented in a separate volume, which physically could stand-alone and which could be handled separately from the remainder of the dossier if necessary.

3.6 The Applicant should indicate any information in Section II-H that he wishes to be treated as confidential, where this is allowed by Community law. The respective confidential and non-confidential parts should be appropriately marked, ideally on each page, and should be bound separately.

4. PRESENTATION OF DATA IN THE MAIN DOSSIER

The information presented in accordance with this Note for Guidance will form Part II-H of the dossier. The entries should be presented in six sections, Part II-H 1 to 6 as follows.

Part II-H: DATA RELATED TO THE ENVIRONMENTAL RISK ASSESSMENT FOR PRODUCTS CONTAINING OR CONSISTING OF GENETICALLY MODIFIED ORGANISMS (GMOs).

Part II-H-1 Introduction

This should include a brief product profile and a description of, and justification for, the proposed release.

Part II-H-2 A copy of the written consent or consents of the competent authorities to the deliberate release into the environment of the Genetically Modified Organisms for research and development purposes where provided for by Part B of Directive 2001/18/EC

Any written consent(s) to release obtained within the Community must be submitted. It would also be useful to submit any written consent(s) to release obtained outside the Community.

Part II-H-3 The complete technical dossier supplying the information requested in Annex III A of Directive 2001/18/EC, including the results of investigations performed for the purposes of research and development

The following points, which are extracts of Annex IIIA of Directive 2001/18/EC, are those which are normally relevant to placing a veterinary medicinal product on the market. The notes in italics indicate where overlap is likely or not likely to occur with entries already required in other sections of the dossier submitted in support of a marketing authorisation, the Part numbers referring to those of the Notice to Applicants for Veterinary Medicinal Products.

The Applicant should add to the particulars listed below any additional items, which are required by the nature or use of the GMO or the proposed release.

Similarly, not all the points included will apply in every case. It is to be expected, therefore, that individual applications will address only the particular subset of considerations, which are appropriate to individual situations.

The level of detail required in response to each subset of considerations is also likely to vary according to the nature and scale of the proposed release.

I. General Information

A. Name and address of the notifier (company or institute)
The name and address of the Applicant should be stated, in the form in which it already appears in Part I of the dossier.

B. Name, qualifications and experience of the responsible scientist(s)

C. Title of the project

II. Information relating to the GMO

A. Characteristic of the recipient or (when appropriate) parental organism

The entries should address each organism (recipient and/or parental organism) as appropriate.

1. Scientific name;
Part IIC 2.1

2. Taxonomy;
Part IIC 2.1.

3. Other names (usual name, strain, name, etc.);
Part IIC 2.1.

4. Phenotypic and genotypic markers;
Part IIC 2.1

5. Degree of relation between donor and recipient or between parental organisms;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

6. Description of identification and detection techniques;
Part IIC, but Applicants should also note this requirement for the environment-specific entries, which are not covered elsewhere in the dossier.

7. Sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques;
Already required for Part IIC, but Applicants should also note this requirement for the environment-specific entries which are not covered elsewhere in the dossier.

8. Description of the geographic distribution and of the natural habitat of the organism including information on symbionts and hosts;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

9. Organisms with which transfer of genetic material is known to occur under natural conditions;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

10. Verification of the genetic stability of the organisms and factors affecting it;
This information is required (for the recipient parental organism) specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

11. Pathological, ecological and physiological traits:
(a) classification of hazard according to existing Community rules concerning the protection of human health and the environment;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(b) Generation tune in natural ecosystems, reproductive cycle;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(c) Information on survival, including seasonability and the ability to form survival structures, e.g. spores;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(d) Pathogenicity: infectivity, toxigenicity, virulence, allergenicity, carrier (vector) of pathogen, possible vectors, host range including non-target organism. Possible activation of latent viruses (proviruses). Ability to colonise other organisms;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(e) Antibiotic resistance, and potential use of these antibiotics in humans and domestic organisms for prophylaxis and therapy;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(f) Involvement in environmental processes: primary production, nutrient turnover, decomposition of organic matter, respiration etc.;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

12. Nature of indigenous vectors:
(a) Sequence;
Part IIC 2.1.
(b) Frequency of mobilisation;
Part IIC 2.I
(c) Specificity;
Part IIC 2.1.
(d) Presence of genes which confer resistance;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

13. History of previous genetic modifications.
Part IIC 2.1.

B. Characteristics of the vector

1. Nature and source of the vector;
Part IIC 2.1.

2. Sequence of transposons, vectors and other non-coding genetic segments used to construct the GMO and to make the introduced vector and insert function in the GMO;
Part IIC 2.1.

3. Frequency of mobilisation of inserted vector and/or genetic transfer capabilities and methods of determination;
Part IIC 2.1.

4. Information on the degree to which the vector is limited to the DNA required to perform the intended function;
Part IIC 2.1.

C. Characteristics of the modified organism

1. Information related to the genetic modification:
(a) Methods used for the modification;
Part IIC 2.1.

(b) Methods used to construct and introduce the insert(s) into the recipient or to delete a sequence;
Part IIC 2.1.

(c) Description of the insert and/or vector construction;
Part IIC 2.1.

(d) Purity of the insert from any unknown sequence and information on the degree to which the inserted sequence is limited to the DNA required to perform the intended function;
Part IIC 2.1.

(e) Methods and criteria used for selection;
Part IIC 2.1.

(f) Sequence, functional identity and location of the altered/inserted/deleted nucleic acid segments in question with particular reference to any known harmful sequence;
Part IIC 2.1.

2. Information on the final GMO:

(a) Description of genetic trait(s) or phenotypic characteristics and in particular any new traits and characteristics which may be expressed or no longer expressed;
Part IIC 2.1, but more data and detail may be required in so far as the data relate to the environmental risk assessment.

(b) Structure and amount of any vector and/or donor nucleic acid remaining in the final construction of the modified organism;
Part IIC 2.1.

(c) Stability of the organism in terms of genetic traits;
Part IIC 2.1.

(d) Rate and level of expression of the new genetic material and method and sensitivity of measurement;
Part IIC2.1.

(e) Activity of the expressed proteins;
Part IIC 2.1.

(f) Description of identification and detection techniques including techniques for the identification and detection of the inserted sequence and the vector;
Part IIC 2.1.

(g) Sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques;
Part IIC 2.1.

(h) History of previous releases or uses of the GMO;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier. See also Part II-H-2.

3. Considerations for human health and animal health, as well as plant health
(a) Toxic or allergenic effects of the non-viable GMOs and/or their metabolic products;
Part III, especially Part IIIE.

(b) Comparison of the modified organism to the donor, recipient or (where appropriate) parental organism regarding pathogenicity;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(c) Capacity for colonisation;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(d) If the organism is pathogenic to humans who are immunocompetent;
- diseases caused and mechanism of pathogenicity including invasiveness and virulence;
- communicability;
- infective dose;
- host range, possibility of alteration;
- possibility of survival outside of human host;
- presence of vectors or means of dissemination;
- biological stability;
- antibiotic-resistance patterns;
- allergenicity;
- availability of appropriate therapies.

The information specified under (v) is required specifically to fulfil the requirements of the environmental risk assessment and may not appear in Part III of the dossier in the detail which is required for the purposes of an environmental risk assessment.

(e) Other product hazards.

III. Information relating to the conditions of release and the receiving environment

A. Information on the release

1. Description of the proposed deliberate release, including its purpose;
This is equivalent to the indications for use of the product and the information provided should be consistent with that stated in Parts IA, IB and IVA.1 of the dossier, in the Summary of Product Characteristics and on the labeling.

2. Foreseen dates of the release and time planning of the experiment including frequency and duration of releases;

3. Preparation of the site previous to the release;

4. Size of the site;

5. Method(s) to be used for the release;
This is equivalent to the indications for use of the product and the information provided should be consistent with that stated in Parts I and IV of the dossier in the Summary of Product Characteristics and on the labeling.

6. Quantities of GMOs to be released;
Part IIA. The quantities of GMO to be administered per dose should be stated.

7. Disturbance on the site (type and method of cultivation, mining, irrigation, or other activities);

8. Worker protection measures taken during the release;

9. Post-release treatment of the site;

10. Techniques foreseen for elimination or inactivation of the GMOs at the end of the experiment;

11. Information on, and results of, previous releases of the GMOs, especially at different scales and in different ecosystems;
Possibly addressed in Part IIID but this information is largely required to specifically fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier, for example the results of the release should include the consequences of any shedding of the virus.

B. Information on the environment (both on the site and in the wider environment)

1. Geographical location and grid reference of the site(s) (in case of notifications under part C, the site(s) of release will be the foreseen areas of use of the product);

2. Physical or biological proximity to humans and other significant biota;

3. Proximity to significant biotopes, protected areas, or drinking water supplies;

4. Climatic characteristics of the region(s) likely to be affected;

5. Geographical, geological and pedological characteristics;

6. Flora and fauna, including crops, livestock and migratory species;

7. Description of target and non-target ecosystems likely to be affected;

8. A comparison of the natural habitat of the recipient organism with the proposed site(s) of release;

9. Any known planned developments or changes in land use in the region, which could influence the environmental impact of the release.

IV. Information relating to the interactions between the GMOs and the environment

A. Characteristics affecting survival, multiplication and dissemination

1.Biological features which affect survival, multiplication and dispersal;
Parts IIIA, IIIC 6.l, IIIC 6.2, IIIE.

2. Known or predicted environmental conditions which may affect survival, multiplication and dissemination (wind, water, soil, temperature, pH etc.);
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

3. Sensitivity to specific agents;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

B. Interactions with the environment

1. Predicted habitat of the GMOs;
Part IIIE.
2. Studies of the behavior and characteristics of the GMOs and their ecological impact carried out in simulated natural environments, such as microcosms, growth rooms, greenhouses, animal houses etc. may also be of relevance to medicinal products;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

3. Genetic transfer capability:
(a) Post-release transfer of genetic material from GMOs into organisms in affected ecosystems;
Partly covered in Part IIIC 6.2 but this information is largely required to specifically fulfil the requirements of the environmental risk assessment and may not necessarily appear in detail elsewhere in the dossier.

(b) Post-release transfer of genetic material from indigenous organisms to the GMOs;
Partly covered in Part IIIC 6.2 but this information is largely required to specifically fulfil the requirements of the environmental risk assessment and may not necessarily appear in detail elsewhere in the dossier.

4. Likelihood of post-release selection leading to the expression of unexpected and/or undesirable traits in the modified organism;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

5. Measures employed to ensure and to verify genetic stability, description of genetic traits which may prevent or minimise dispersal of genetic material and methods to verify genetic stability;
This entry should include detailed information specifically relevant to the environmental risk assessment and should if necessary be more extensive than that presented in Part IIC 2 of the dossier.

6. Known routes of biological dispersal or potential modes of interaction with the disseminating agent, including inhalation, ingestion, surface contact etc.;
Part IIIA 1, IIIC 6.1, IIIC 6.2, IIIE.

7. Description of ecosystems to which the GMOs could be disseminated;
Parts IIIA, IIIE.

8. Potential for excessive population increase in the environment;
Part IIIE.

9. Competitive advantage of the GMOs in relation to the unmodified recipient or parental organism(s);
Part IIIE.

10. Identification and description of the target organisms if applicable;
Parts IIIA 1, IIIC 6.1, IIIE.

11. Anticipated mechanism and result of interaction between the released GMOs and the target organism if applicable;
Part IIIE.

12. Identification and description of non-target organisms which may be adversely affected by the release of the GMO, and the anticipated mechanism of any identified adverse reactions;
Parts IIIA 1, IIIC 6.1, IIIE.

13. Likelihood of post-release shifts in biological interactions or in host range;
Part IIIE.

14. Known or predicted effects on non-target organisms in the environment, impact on population levels of competitors, hosts, symbionts and pathogens;
Part IIIE.

15. Known or predicted involvement in biogeochemical processes;
Part IIIE.

16. Other potential interactions with the environment;
Part IIIE.

V. Information on Monitoring, Control, Waste Treatment and Emergency Response Plans

A. Monitoring Techniques

1. Methods for tracing the GMOs, and for monitoring their effects;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

2: Specificity (to identify the GMOs, and to distinguish them from the donor, recipient or, where appropriate, the parental organisms), sensitivity and reliability of the monitoring techniques;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

3. Techniques for detecting transfer of the donated genetic material to other organisms;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

4. Duration and frequency of monitoring.

B. Control of the release

1. Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release or the designated areas of use;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier, and is likely to be relevant in the case of vaccines disseminated as a baited formulation in an open environment.

2. Methods and procedures to protect the site from intrusion by unauthorised individuals;

3. Methods and procedures to prevent other organisms from entering the site.

C. Waste treatment

1. Type of waste generated;
Parts IIIA l, IIIC 6.2, IIIC 6.3.

2. Expected amount of waste;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

3. Description of treatment envisaged;
Part IB, but this information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

D. Emergency response plans

1. Methods and procedures for controlling the GMOs in case of unexpected spread;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier, and is likely to be relevant in the case of vaccines disseminated as a baited formulation in an open environment.

2. Methods for decontamination of the areas, e.g. eradication of the GMOs;
This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier, and is likely to be relevant in the case of vaccines disseminated as a baited formulation in an open environment.

3. Methods for disposal or sanitation of affected by the spread;

4. Methods for the isolation of the areas affected by the spread;

5. Plans for protecting human health and the environment in case of the occurrence of an undesirable effect;
Part IB, but this information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

Part II-H-4. The environmental risk assessment resulting from the information provided under points II-H-1 to II-H-3 above

The assessment of environmental risk should follow logically from the data presented in II-H-1 to II-H-3. Risks to human health, non-target animals, soil, water, air, individual ecosystems etc. should be addressed as appropriate. This section should be compiled in accordance with the Note for Guidance on the Conduct of the Environmental Risk Assessment for Veterinary Medicinal Products Containing or Consisting of GMOs .

Part II-H-5. Conclusion

The Applicant should present his overall conclusions.

5. PRESENTATION OF PARTICULARS IN THE EXPERT REPORTS

Part II-H of the main documentation should be addressed in the Analytical (Chemical, Pharmaceutical and Biological or Microbiological) Expert Report and should include a critical evaluation, the opinion of the expert as to whether sufficient guarantees have been provided as to the suitability of the product for its proposed use, and an appendix containing a summary of all the important data. The expert should compile entries in accordance with the general requirements for Expert Reports outlined in the Notice to Applicants. In particular, the expert should be appropriately qualified.

B. GUIDELINE FOR THE CONDUCT OF THE ENVIRONMENTAL RISK ASSESSMENT FOR VETERINARY MEDICINAL PRODUCTS WHICH CONTAIN OR CONSIST OF GENETICALLY MODIFIED ORGANISMS

1. BACKGROUND AND INTRODUCTION

This guidance concerns the environmental risk assessment needed to comply with the requirements of Article 28(2) of Council Regulation 2309/93 on the licensing of veterinary medicinal products which contain or consist of Genetically Modified Organisms (GMOs). The Regulation makes provision for an environmental risk assessment similar to that in Directive 2001/18/EC on the Deliberate Release into the Environment of GMOs. In both this Directive and in the Regulation, the environmental risk assessment is derived from the technical dossier containing the information required under Annex II and III of the Directive. Under Council Regulation 2309/93 therefore, the environmental risk assessment should be a reasoned statement of the overall risk of damage to human health and to the environment from the proposed marketing of a veterinary medicinal product containing or consisting of a GMO.

There are no hard and fast rules for risk assessments. The following guidance outlines the generally accepted terminology for a risk assessment and includes some practical steps and a workable format to aid Applicants.

The level of detail to be considered in a risk assessment will depend on circumstances. It will be lower, for example, where it is immediately obvious that the hazards, and hence the consequent risks, are low or that the proposed control measures are clearly adequate to limit the contact of the product with humans and the environment.

2. SCOPE OF THE GUIDELINE (Types of products)

This guidance has been based largely on the considerations appropriate to what will probably be the most likely type of veterinary medicinal products containing or consisting of GMOs capable of replication or of transferring genetic material, namely: live viral, bacterial or parasitic vaccines, including vector vaccines.

3. ENVIRONMENTAL RISK ASSESSMENT

3.1 General considerations

For veterinary medicinal products it may be appropriate first to consider the risks to human health and to address whether it is necessary to take certain measures to control the risks arising from the administration and use of the product. The potential risks to the environment should then be assessed on the basis that those control measures are in place.

The main considerations for the risks to human health will be determined by whether or not the GMO is a zoonotic agent, or likely to be a zoonotic agent taking into account the characteristics of the parental organism, any organisms used as donors and the possibility of changes in host range, pathogenicity or tropism, as a result of the genetic modifications. The classification system for pathogenicity of micro-organisms as set out in Council Directive 90/679/EEC, as amended, may provide a useful reference for these considerations.

To all intents and purposes, the human health part of the environmental risk assessment considers the risk to human health as if humans were a sub-set of the wider environment, or another non-target species. The human risk assessment must include consideration of the risk to those who handle or administer the product and or treated animals, risks to relatives and other contacts of these operators and risk to the general public. It will be necessary to consider the possible effects on healthy humans as well as to more vulnerable individuals (the young or old, immuno-compromised, pregnant women or otherwise susceptible). For example, the increasing incidence of people who are receiving immuno-

suppressants, or have recently undergone chemotherapy, or who have developed AIDS may mean that there is a section of the population who are at greater risk and this needs to be taken into account at each stage of the risk assessment.

3.2 Sources of information

The risk assessment is intended as an overall statement reflecting all the information contained in the dossier.

Although wherever possible the risk assessment should: be based on quantifiable outcomes, it is recognised that many of the judgements must necessarily be qualitative. Any statements or assertions in the assessment should, however, be supported by some evidence, quantitative where possible.

How much information is needed in any particular point will depend on its importance in the assessment and the extent to which it is generally accepted material. There is no need to spell out in great detail what is included elsewhere in the dossier or in textbooks or literature. However the logic of the argument should be clear and enough justification should be included on any unusual or particularly important points for the assessment to be testable. Note that it is always permissible to assume the worst and act accordingly if the cost of gathering the information (by experimentation or review) for a more precise assessment is disproportionate.

4. FRAMEWORK FOR RISK ASSESSMENT

The aim of the risk assessment is to identify hazards, to estimate the likelihood that the hazards will lead to actual harm and to take decisions regarding the appropriate control measures. The main elements of a risk assessment are therefore:

(i) hazard identification;
(ii) assessment of the likelihood that the hazard will occur;
(iii) assessment of exposure to the hazard and the consequences of that exposure;
(iv) assessment of the level of risk by consideration of the severity of any adverse consequences and the likelihood that they will occur;
(v) selection and assignment of appropriate control measures (risk management).

4.1 Assessment of risk to humans

4.1.1 Hazard identification

In the context of this guidance, hazards are defined as those features of the GMO which have the potential to cause harm, either directly (such as infection) or through some form of possible event (such as the transfer of hazardous genes to and from other organisms). It is important to be exhaustive in the identification of possible hazards and not to discount at this stage any of the hazards given below on the basis that they are unlikely to occur. The assessment of possible exposure and likelihood are separate stages of the assessment process.

This stage of the assessment should aim to identify all possible adverse effects on humans and should include the following:

4.1.1.a Pathogenicity or other adverse effects

With respect to humans and animals, details of the pathogenicity of the parental organism and the GMO itself will have been considered during the safety studies on the product. When determining the hazards associated with the GMO, consideration should be given to the pathogenicity and virulence, any changes to the host range or tissue tropism and, if it is still potentially pathogenic, whether the GMO is susceptible to available therapies or is expected to exhibit altered interactions with host defense mechanisms. As well as the possibility of infection in healthy individuals, the possibility of infection in immuno-compromised or other especially susceptible individuals should be identified.

4.1.1 b Genetic instability (especially attenuating mutations)

Consider whether the GMO is stable over repeated generations and, in particular, whether any genetic instability could affect attenuating mutations or alter the behaviour of the GMO, particularly if it could result in a reversion to virulence. The type of attenuating mutation (point mutation or deletion) will be an important consideration in assessing the likelihood of the hazard occurring. Attention should be paid to those bacterial GMOs if potentially transferable vectors based on plasmids, bacteriophages or transposons have been used.

4.1.1.c Gene transfer

Gene transfer may be considered a hazard under some circumstances, for example if it could result in the spread of genes to other organisms with potentially undesirable consequences. In some senses it can be considered as a subset of genetic stability.

4.1.1.d Survival /dissemination

The ability of the GMO to survive for long periods in the environment (for example in the litter of the poultry house or grazing pastures) may constitute a hazard under some circumstances, for example if it could mean that there is a greater likelihood of contact with individuals. This may be further compounded if survival offers an increased possibility of wide spread dissemination by water or other routes or by any arthropod or animal vectors.

4.1.2. Assessment of the degree of exposure and the likelihood of the hazard occurring

In order to determine the risk posed by the GMO it will be necessary to determine the likelihood of any of the above hazards occurring, i.e. whether people will be exposed to the hazard associated with a GMO and, if so, whether they would suffer an adverse effect.

4.1.2.a Potential for exposure to the GMO in the product

At this stage, it will also be necessary to consider whether everyone exposed to the GMO would suffer an adverse effect or whether any adverse effect would occur in only a small proportion of exposed individuals. Infrequent adverse effects may be either due to a low probability of an effect occurring in any given individual or because a small proportion of the population is susceptible. The latter may include immuno-compromised individuals or those with a particular vaccination status or on an antibiotic regimen.

One important component of this factor is whether the wider environment (including other humans) comes into contact with the GMO in the product under normal circumstances (i.e. are exposed to the GMO). The degree of exposure of operators will have a bearing on the likelihood of a hazard occurring. When considering the degree of exposure of operators and their relatives and contacts and the general public to the product, the following matters should be taken into account.

(i) Type of packaging and procedures before and after administration

Most, if not all, veterinary medicinal products containing GMOs will be securely packaged on receipt and the packaging should allow any initial preparatory steps (e.g. reconstituting freeze-dried preparations) to be undertaken in a safe and aseptic manner. However, the proposed method of preparation and administration will have a bearing on the degree of exposure of operators to the GMOs and needs to be considered. For example, single dose preparations for administration to a companion animal in the surgery is likely to result in less exposure than mass medication of farm animals. It may be appropriate to consider who is likely to administer the product (veterinary surgeon or farmer) and the likelihood of any necessary instructions for safe use of products being achievable. It will also be necessary to consider whether or not unused product can be readily disposed of in a reliably safe manner.

(ii) Route of administration (parenteral vs. oral vs. oculo-nasal vs. spray)

It may be expected that there is more opportunity for exposure of the operator to the product organisms when the product is administered by spray, orally or oculo-nasally, than by injection but the risks of self-injection must be borne in mind.

(iii) Shedding of live product organisms (route, numbers, duration)

The extent to which the product organisms multiply in the host, can be excreted and spread will have been studied as part of the safety studies. Many products may well consist of attenuated or replication defective organisms and the likelihood of exposure will be less than that associated with the wild type, parental strain.

The overall degree of exposure of humans such as animal attendants should be indicated. It should be noted that high exposure does not necessarily mean high risk and conversely, that even 'low' exposure, but with severe consequences, may lead to an unacceptable risk.

It is recommended that the possibility of exposure and likelihood of hazards occurring is qualitatively judged as either ‘negligible’, ‘low’, ‘moderate’ or ‘high’.

4.1.3 Assessment of level of risk

Having identified any hazards and assessed the degree and likelihood of exposure and the consequences of that exposure it is necessary to evaluate the risk associated with each hazard. Risk is generally held to be the product of exposure likelihood and consequence. It is inevitably always going to be difficult to ‘multiply’ qualitative statements such as ‘high’ and ‘low’, but Table 1 should help this process. The risk matrix is not definitive and there will always be some scope for flexible, case by case evaluation. In many cases, it will be necessary to decide between one of two outcomes and, as in the earlier parts of the process, some justification for the choice should be provided. In addition, a range of risks may be apparent if more than one hazard is being evaluated. There will, therefore, be a need to make an overall assessment of the risk taking all factors into consideration.

Once an overall assessment of the risk associated with each hazard has been produced, it will be necessary to evaluate the significance of the risk. It is generally considered that any risk other than ‘effectively zero’ or ‘low’ is unacceptable without some consideration of measures and proposals to control the risks to human health.

4.1.4 Consequences of a hazard occurring

This stage of the assessment should consider, for each identified hazard, what is the result of the hazard occurring i.e. what effect it may have on an exposed individual or population. It is anticipated that the range of consequences will fall between those that are negligible and self limiting and those that would be severe, either having an immediate and serious effect or possibly leading to long term, harmful consequences.

It is suggested that the consequences of each hazard be indicated qualitatively as ‘negligible’, ‘low’, ‘medium’ or ‘severe’. An adverse effect may be either immediate or delayed. Immediate and relatively trivial effects such as sero-conversion in casual contacts may be extremely easy to identify but may not be particularly important. However, longer term and less obvious effects, such as oncogenicity or toxicity, will clearly be difficult to assess but extremely important.

The assessment of the consequences of a hazard occurring will need to consider the effects on individuals as well as the overall community. For each hazard it may be necessary to split the considerations into the ‘worst case’ and the ‘normal case’. During the overall assessment of the level of risk,' such differences should then be weighed up in arriving at the final risk assessment. For example, the consequences to rare individuals may be judged to be ‘serious’. However, because such individuals do not form a large part of the community (and therefore the likelihood of the hazard occurring is low), the risk associated with the particular hazard may be acceptable.

4.1.5 Control of risk

This stage of the risk assessment will require some consideration of the particular aspect of the assessment, which leads to an unacceptable level of risk. For example, if it were caused by a lack of detailed knowledge on a particular hazard, then it might be necessary to acquire further information, either by experimentation or from published literature. Alternatively, it could be that changes to the

instructions for use or to any recommended precautions would reduce the level of exposure to staff or other people. In any case, personnel, such as those administering the product and those handling the animals at the time, will be subject to worker protection legislation such as the Biological Agents Directive (90/679/EEC as amended by 93/88/EEC), requiring, amongst other things, risk assessment and appropriate control measures.

4.2 Assessment of the risks to the environment

Having decided on the controls (if any) that are appropriate in order to minimise the risks to humans, it is necessary to evaluate whether there could be any adverse effect on the environment resulting from the use of the product. The characteristics of the GMO need to be considered, particularly its host range and pathogenicity. Account must be taken of the characteristics of the parental organism, any organisms used as donors and the possibility of changes to host range, pathogenicity or tropism as a result of the genetic modifications.

The objective of the environmental part of the risk assessment is to determine the probability of adverse consequences or 'harm' to the environment. Harm results if hazards are realised. The steps are, in principle, as for the human health part of the risk assessment, but the particular considerations are of course different.

4.2.1 Hazard identification

The starting point for risk assessment is to identify the characteristics of the GMO, which are a hazard because they have the potential to cause harm in the receiving environment. Appropriate information about the recipient or parental organism and the donors, as well as information about the GMO itself, should be considered.

4.2.1.a Capacity to transmit to non-target species

The specificity of the host range is very important for veterinary products. Any likely changes as a result of the genetic modification should be taken into account.

4.2.1.b Shedding of live product organisms (route, numbers, duration)

The extent, to which the product organisms multiply in the host, can be excreted and spread will have been studied as part of the safety studies. Many products may well consist of attenuated or replication defective organisms and the likelihood of exposure will be less than that associated with the wild type, parental strain. However, the potential for organisms passaged from animal to animal to become less attenuated must be taken into consideration.

4.2.1.c Capacities to survive, establish and disseminate

This is also a key consideration if an organism is not capable of surviving, for example because of multiple disablement, as other hazards are then likely to be minimised. The risk assessment could be completed at this stage if the risks to the environment are low or effectively zero. However, if it is likely that the organism could survive for a sufficiently long period for it to cause harm, and possibly establish and disseminate in the environment, then not only this hazard but also other hazardous characteristics need to be considered.

4.2.1.d Potential for gene transfer

Although most organisms have the ability to transfer genes, some do not. Consider, in particular, the extent to which the method of modification might increase the potential for transfer as, for example, in the case of non-integrating viral vectors.

4.2.1.e Products of expression of inserted sequences

Identify all products of gene expression that could cause harm, bearing in mind that an inserted gene might code for a product that is toxic, or otherwise detrimental, to other organisms. Consider the extent to which those products could have an effect on other organisms.

4.2.1.f Phenotypic and genotypic stability

Consider whether genes inserted into the GMO on extra-chromosomal elements might be transferred more readily and the extent to which genotypic instability might lead to phenotypic instability.

4.2.1.g Pathogenicity to other organisms

The pathogenic properties of many organisms used as recipient or parental organisms are well documented and these should be identified, if appropriate. Consider whether a change in host range could occur as a result of the genetic modification, which has been undertaken.

4.2.1.h Potential for other effects

Consider whether the GMO might have the potential to exert other effects such as the transmission and replication of viruses in other organisms as a result of trans-capsidation and the effects of recombination.

4.2.2 Assessment of likelihood

The next step is to estimate the likelihood (probability and frequency) of hazard(s) being manifested. A key factor in determining this is the potential receiving environment. This includes the wider as well as the local environment in which the product is intended, or likely, to be used.

Particular characteristics of the local environment that could contribute to manifestation of the hazard should be identified and assessed. Climatic, geographical and soil conditions, demographic considerations, the types of flora and fauna in the potential receiving environment are some of the important ones.

Consideration should be given to any potential exposure of the living and non-living environment to the GMOs and the magnitude and duration of such exposure. When estimating probabilities and frequencies, consideration should include the number of organisms that might reach the environment since the probability that a hazard will be realised will often be influenced by the number of viable organisms in the environment due, for example, to excretion. For the hazard ‘survival capacity’, therefore, it is appropriate to assess the proportion of the GMOs that are likely to survive. In the case of the likelihood of gene transfer, the probable number of such events or the extent to which transfer will occur should be considered. If the GMO has pathogenic characteristics, assess the proportion of target organisms in the environment likely to be affected, including taking into consideration, the likelihood of the GMO to spread to, or reach, these organisms.

The mode of administration might have an impact on the likelihood that hazard(s) will be manifested. For example, spray or other forms of mass administration are more likely to lead to the introduction of the GMO into the environment than if given by injection. Likelihood should be expressed as ‘high’, ‘medium’, ‘low’ or ‘negligible’.

4.2.3 Assessment of level of risk

Having judged the magnitude of harm if the hazard were to be realised, and the likelihood or frequency of such harm being caused, the level of risk is assessed by considering the combined effect of these two components.

This should be carried out for each of the hazards identified. The matrix in Table 1 used for the human health part of the risk assessment can be used again to come to an evaluation of the environmental risk for each environmental hazard.

4.2.4 Assessment of the consequence

For each hazard of the GMO identified, whenever it is possible or probable that the GMO in the product will reach the environment, it must be considered whether that environment would cause or allow the hazard to be realised. Thus again, the characteristics of the potential receiving environment

need to be considered.

An assessment of the magnitude of harm is based on the assumption that the hazard will be realised. Inevitably there will be a degree of judgement in making the assessment, but the consequences should be described as ‘severe’, ‘medium’, ‘low’, or ‘negligible’. A ‘severe’ consequence might be a major change in the numbers of one or more species leading to negative effects on the functioning of the ecosystem and/or other connected ecosystems. It is unlikely that the changes would be reversible. A 'low' consequence might be if any change in population densities is such that it has no negative effects on ecosystem function and no impact on endangered or beneficial species.

The above illustrations reflect the potential effect of the GMO on populations. In some cases, however, it may be more appropriate to consider the likely effects on individual organisms; for example endangered mammals. In most cases it should be possible to use the guidelines to assess in qualitative terms the degree of harm which a particular GMO might cause.

4.2.5 Selection and assignment of appropriate control measures (risk management)

If the environmental risks are not as low as reasonably practicable, the process of risk assessment in relation to that hazard should be repeated to ascertain whether the application of additional management techniques could reduce the level of risk. Consideration might be given, for example, to limiting the proposed routes of administration to those likely to lead to a lower level of risk.

5. SUGGESTED FORMAT FOR PRESENTATION OF THE CONCLUSIONS OF THE RISK ASSESSMENT

Applicants may find the following structure useful to record their risk assessment.

1. Summary

Summary of the overall risk of damage to the environment (including human health) from the proposed marketing of the GMOs forming the subject of the application.

2. Assessment of risk to humans

2.1. Hazard identification: Hazardous characteristics of the GMO that could, in certain circumstances, lead to harm in humans:
a. Pathogenicity or other adverse effects
b. Genetic instability (especially attenuating mutations)
c. Gene transfer
d. Survival/dissemination

2.2. Assessment of the degree of exposure and the likelihood of each hazard occurring

2.3. Assessment of level of risk

2.4. Consequences of a hazard occurring
Assessment of the overall risk of harm to humans (the total risk after consideration of the risk of each of the hazards occurring): High, medium, low, effectively zero.

3. Assessment of the risk to the environment

3.1. Hazard identification. Hazardous characteristics of the GMO that could, in certain circumstances, lead to harm to the environment:
a. Capacity to transmit to non-target species
b. Shedding of live product organisms (route, numbers, duration)
c. Capacities to survive, establish and disseminate
d. Potential for gene transfer
e. Products of expression of inserted sequences
f. Phenotypic and genotypic stability

g. Pathogenicity to other organisms
h. Potential for other effects

3.2. Assessment of likelihood

3.3. Assessment of level of risk

3.4. Assessment of the consequence

3.5. Assessment of the overall risk to the environment (the total risk after consideration of the risk of each of the hazards occurring):
high, medium, low, effectively zero.

4. Assessment of the overall risk

Assessment of the overall risk to humans and the environment (from Points 2.5 and 3.5 above).

Table 1
ESTIMATION OF RISK

Consequence of hazard	Likelihood of Hazard			
	High	Moderate	Low	Negligible
Severe	High	High	Medium	Effectively Zero
Medium	High	High	Medium/Low	Effectively Zero
Low	Medium/Low	Low	Low	Effectively Zero
Negligible	Effectively Zero	Effectively Zero	Effectively Zero	Effectively Zero

This matrix is not intended to be definitive, but illustrative of the way in which an estimate of risk might be obtained from the consequence and likelihood that a hazard will be realised. Different components may be differently weighted, however, depending on the knowledge and experience of the GMO and operation involved.

C. GUIDANCE ON THE INTEGRATION OF THE EVALUATION OF THE ENVIRONMENTAL RISK ASSESSMENT WITH THE EVALUATION OF THE REST OF THE APPLICATION FOR MARKETING AUTHORISATION FOR A MEDICINAL PRODUCT CONSISTING OF OR CONTAINING LIVE GENETICALLY MODIFIED ORGANISMS

1. INTRODUCTION

The particulars and documents required in support of an application for a marketing authorisation for such a medicinal product will include an environmental risk assessment and related information, in accordance with Article 28.2 of Council Regulation (EEC) No. 2309/93.

The authorisation procedure, which is laid down in the Regulation, is mandatory for such medicinal products containing live GMOs, since they fall within the scope of Part A of the Annex.

The key principles in the evaluation procedure of a medicinal product containing a live GMO are as follows:

2. APPLICATION DOSSIER

The application is submitted to the EMEA in accordance with the current version of the Standard Operating Procedure (SOP) on the SUBMISSION OF AN APPLICATION FOR THE GRANTING OF A COMMUNITY MARKETING AUTHORISATION.

In the case of a medicinal product consisting of, or containing, a live GMO, the dossier will include (Article 28.2 of the Council Regulation (EEC) No. 2309/93):

- a copy of written consents issued by the competent authorities to the deliberate release of GMOs for research and development purposes;
- the results of any investigations performed for the purposes of research and development;
- the complete technical dossier supplying the information as set out in Annexes IIIA of Directive 2001/18/EC;
- the environmental risk assessment resulting from this information.

3. PRESUBMISSION

An Applicant may seek advice from the Agency within its Committees on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products. Usually the Committee concerned will appoint one of its members to co-ordinate the advice to be given. Advice may also be sought on the fulfillment of the requirements of Article 28.2 of Council Regulation N° (EEC) 2309/93. Applicants may seek advice on applications prior to submission. *See appropriate section in the Notice to Applicants on advising Applicants on the conduct of various tests and trials necessary to demonstrate the quality, safety and efficacy of: medicinal products. (Article 51 of the Regulation).*

See also SOPs EMEA/CVMP/036/97- REVISION and EMEA/CVMP/036/97- REVISION

4. EVALUATION

During the evaluation the Rapporteur shall hold the necessary consultations in a timely manner with the bodies set up in accordance with Directive 2001/18/EC . The conclusions and results of any consultation will be included in the Rapporteur's assessment report, including requests for clarification or further information.

The CVMP will give its opinion within 210 days of the receipt of a valid application. The opinion shall respect the environmental safety requirements resulting from the risk assessment on the basis of Directive 2001/18/EC to ensure that appropriate measures are taken to avoid the adverse effects on human health and the environment which might arise from the deliberate release or placing on the market of a medicinal product containing live GMOs. In order to provide its Opinion, the CVMP shall

carry out the evaluation according to the following timetable:

Day 1

Once the application has been validated, the EMEA Secretariat will send a copy of the timetable to the CVMP Chairman and Members, the Applicant and the Competent Authorities under Directive 2001/18/EC. These Competent Authorities will be given the opportunity to request Part II.H of the application dossier from the Applicant. This request will be channeled via the EMEA Secretariat and a deadline for requests of copies will be set in order to facilitate the copying of large volumes of documentation by the Applicant.

Day 1 – 70

The risk assessment submitted with the application will be considered in conjunction with the assessment of quality, safety and efficacy according to the requirements laid down in the Annex to Council Directive 81/852/EEC, as amended, and will be assessed by the Rapporteur, Co-Rapporteur or their Experts. Copies of the Rapporteur's assessment on *this part* of the application will be sent to the Competent Authorities under Directive 2001/18/EC by the Secretariat (on Day 70).

Day 70 –90

The Competent Authorities under Directive 2001/18/EC will be asked to provide any questions they may have on the dossier or assessment by Day 90 to the Rapporteur or such person designated by the Rapporteur, with a copy of any questions to the EMEA Secretariat.

Day 90 – 119

The Rapporteur, or such person designated by the Rapporteur, will decide on the inclusion, or not, of any questions from the Competent Authorities under Directive 2001/18/EC in the draft CVMP List of Questions. The questions submitted by these Competent Authorities will be tabled and discussed at the Rapporteur’s meeting to be held on Day 119.

Day 120

Once the CVMP List of Questions has been adopted, the EMEA Secretariat will extract from the List of Questions those questions raised on Part II.H of the application. This extract will be forwarded to the Competent Authorities under Directive 2001/18/EC by the Secretariat.

Day 150

The section of the joint Rapporteur/Co-Rapporteur assessment report on the Applicant's answers to questions on Part II.H of the dossier will be forwarded to the Competent Authorities under Directive 2001/18/EC by the Secretariat.

Day 180

Should the clock be stopped and the Applicant invited to attend an oral explanation, the Competent Authorities under Directive 2001/18/EC will be informed of any issues on Part II.H of the dossier that are to be further clarified.

The outcome of the oral explanation will be communicated to the Competent Authorities under Directive 2001/18/EC where this is appropriate.

Day 210

The final conclusion remains with the Committee, having assessed the quality, safety and efficacy data provided by the Applicant in support of the product, shall discuss the risk versus the benefit of the use of the product and shall recommend or not the granting of a Community Marketing Authorisation.