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MARKETING AUTHORISATIONS FOR VETERINARY MEDICINAL PRODUCTS

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www.gov.uk

QUICK START GUIDE

This Veterinary Medicines Guidance Note (VMGN) is aimed primarily at members of the pharmaceutical and biological industries, and at those companies and individuals involved in the development and marketing of veterinary medicines, who wish to obtain a Marketing Authorisation (MA) for a Veterinary Medicinal Product (VMP).

The quick start guide is a summary of the provisions of the Veterinary Medicines Regulations (VMR), detailed information is found in the body of the guidance note.

- The requirement to obtain an MA before placing a VMP on the market for sale and supply is a legislative provision in the VMR.
- A VMP must be the subject of a valid MA, granted by the Veterinary Medicines Directorate (VMD) or by the European Commission (EC), before it can be placed onto the UK market for sale and supply. The Marketing Authorisation Holder (MAH) has to market that product in compliance with the terms of the authorisation. The VMR does, however, permit certain medicinal products to be marketed without the need for an MA under Schedule 6 - Exemptions for small pet animals. Further information can be found in VMGN 12.
- There are a number of different routes to obtaining an MA; these routes determine the procedures, processes and timelines used in progressing an application for a new MA in accordance with legislation. Once granted, the authorisation will be classified as nationally authorised, centrally authorised or mutually recognised. MAs granted by other European Union (EU) Member States (MSs) are not valid in the UK, they only allow the product in question to be marketed by the MAH in that MS.
- Within these routes, there are several different legal bases upon which an application for an MA may be made, which determine the type and content of the data submitted in support of the application.
- Once an application for a new MA has been progressed, and the benefit:risk assessment is considered positive, the MA will be granted. Not all products for which applications are submitted are granted an MA. Some applications for an MA are refused at the end of the assessment process due to insufficient and/or inadequate supportive data.
- Following grant of an MA, the authorisation may be subject to a number of post-authorisation requirements including reassessment or renewal of the MA, and variation procedures that facilitate any proposed changes to the particulars of an MA.

FURTHER INFORMATION

- Further information is available from the VMD, Woodham Lane, New Haw, Addlestone, Surrey, KT15 3LS - Tel: +44 (0)1932 336911, Fax: +44 (0)1932 336618 or e-mail: VMGNotes@vmd.defra.gsi.gov.uk. VMGNs and other information, including details of VMD contacts, are available on the VMD website (www.vmd.defra.gov.uk).

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Introduction

1. This is one of a series of Veterinary Medicines Guidance Notes (VMGNs) explaining the requirements for Marketing Authorisations (MAs) under the Veterinary Medicines Regulations (VMR), which are revoked and replaced on a regular basis, so any references to them should be read as referring to those currently in force. Therefore, the date and number of the Statutory Instrument are not shown in this VMGN. The VMGN will be updated as necessary and the date of the most recent update is shown on the front cover.
2. The VMR set out the UK controls on veterinary medicines including their manufacture, advertising, marketing, supply and administration. For further information please refer to VMGN 1 Controls of Veterinary Medicines, which is published on the VMD's website
http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx
3. This VMGN provides guidance on applying for an MA, renewal of an MA, and any subsequent changes to it known as 'variations'. This is a complex area and this guidance has been written to cover the majority of possible scenarios; it is not possible to cover everything in the guidance, so we encourage readers to contact the Veterinary Medicines Directorate (VMD) if they require further information.
4. It should be noted that, except for mention in Chapter 1, guidance about centrally authorised products is not provided in this VMGN. Centrally authorised products are managed by the European Medicines Agency (EMA) in London. More information about centrally authorised MAs is available on the EMA website:
www.ema.europa.eu
5. Reference to European Union (EU) Member States (MSs) should be read to include all EU MSs as well as Norway, Lichtenstein and Iceland.
6. Unless otherwise specified, all documents available on the VMD website will be found in the thematic area - 'Pharmaceutical Industry'.
7. A list of Veterinary Medicinal Products (VMPs), subject to a valid MA in the UK, is available in the product information database on the VMD website:
<http://www.vmd.defra.gov.uk/ProductInformationDatabase/>
8. A VMP must be the subject of a valid MA, issued by the VMD or by the European Commission (EC), before it can be placed onto the UK market for sale and supply. The Marketing Authorisation Holder (MAH) has to market that product in compliance with the terms of the authorisation.
9. A product may only be marketed in the UK if it is subject to a valid MA as issued by the VMD or EC; MAs issued by another EU MS are not valid in the UK; they only allow the product in question to be marketed by the MAH in that MS.

CHAPTER 1

What is a Marketing Authorisation?

Introduction

10. All MAs include a Summary of Product Characteristics (SPC) and product literature, e.g. labels. The purpose of the SPC is to provide a clear and unambiguous description of the approved conditions of use of a VMP; it includes information such as the active substance, target species, withdrawal periods etc. Further information about SPCs and product literature is available in Chapter 7.
11. An application for an MA should normally be made by the proposed MAH who must be established within the EU. For companies this means they must be formed in accordance with the law of a MS and have their registered office, central administration, or principle place of business within the EU.
12. Not all products for which applications are submitted are granted MAs. Some applications for an MA are refused at the end of the assessment process either due to insufficient and/or inadequate supportive data, or after assessment of all the data provided in support of the application, a negative benefit:risk conclusion is reached.

The Vm Symbol

13. An authorised product will have an authorisation number preceded by the symbol Vm on its product literature, e.g. labels; this offers users a clear guarantee that the VMP has been assessed and approved in accordance with the instructions on the product literature. It should be noted that a product subject to an MA issued by the EC will not have the Vm symbol on its product literature instead an identifier with the following format will be used - EU/2/01/011/001.

Distribution Categories

14. An authorised product will also have a distribution category, which relates to the retail supply of a VMP, e.g. a product classified as Prescription Only Medicine - Veterinarian (POM-V) may only be supplied by a veterinary surgeon or a pharmacist and must be supplied in accordance with a prescription from a veterinary surgeon. For further information please refer to VMGN 3 - Guidance for Retailers which is published on the VMD's website http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

Validity of an MA

15. An MA (excluding exceptional MAs) is valid for five years following grant of the initial MA. After this time the MA must be renewed in order for it to continue to be authorised. If an MA is not renewed by the renewal date it will cease to be valid.
16. Once renewed the MA will remain valid indefinitely unless the VMD considers that an additional renewal is justified on the grounds of pharmacovigilance, five years after the first renewal, or unless the MA is revoked or expired. Further information about renewals is available in Chapter 5.

17. Where an authorised product is not marketed in the UK for three consecutive years, the authorisation will cease to be valid unless, exceptionally, an exemption from this provision is granted on justified human or animal health grounds. Such an exemption might be granted, for example, where a product for treating a sporadically occurring disease had not been marketed because the disease had not occurred during that period. Information on marketing will be received under the pharmacovigilance procedures. This provision is known as the 'sunset clause'; the VMD will contact MAHs about products subject to the sunset clause in order to discuss a way forward and before taking any action.
18. During the validity of the MA, evidence may become available which throws doubt on the safety, quality or efficacy of the product, or which alters the benefit:risk assessment. In such circumstances the VMD may revoke, suspend or compulsorily vary the authorisation. The circumstances in which such action can be justified are specified in the VMR. It should be noted that if the VMD becomes aware that an MAH has changed any of the approved specifications of an authorised product without the prior approval of the VMD (except in the case of a Type IA variation) the MA will be suspended immediately. The suspension will remain in force until the changes have been approved, or the product is brought into line with the authorisation.

Authorisation Routes

19. There are four different routes to obtaining an MA; these routes determine the procedures, processes and timelines used in progressing an application for a new MA in accordance with legislation. Once granted, the authorisation will be classified as nationally authorised, centrally authorised or mutually recognised.

Authorisation Route

Authorisation Type

A national procedure

The product will be classed as "nationally authorised".

The Centralised procedure

The product will be classed as "centrally authorised".

The Mutual Recognition procedure

The product will be classed as "mutually recognised".

The Decentralised procedure

The product will also be classed as "mutually recognised".

20. It should be noted that a product authorised by either the mutual recognition or decentralised procedure will end up being 'mutually recognised'.

Nationally Authorised Products

21. A product that has been assessed and approved on a national basis only, i.e. there has been no interaction with other EU MSs.

Centrally Authorised Products

22. A centrally authorised product is one that has been assessed and approved on a community level involving all EU MSs, i.e. evaluated via the centralised procedure and approved by the EC. A pan-European authorisation is issued permitting the marketing, sale and supply of the product in all EU MSs including the UK.
23. The EMA organises the process of evaluation using scientific expertise from all EU MSs. If a positive opinion is given by the EMA after a product has been evaluated, it is sent to the European Commission (EC). If the EC also has a favourable opinion, it makes a formal decision to authorise the product and it grants a single MA that is valid in all EU MSs. Note, whilst the EC will usually endorse a positive opinion, it has the right to reject it.
24. Although the VMD does not issue an MA for products authorised by the centralised procedure, the outcome is the same: the product is authorised for use in the UK.
25. The centralised procedure is compulsory for some products and optional for others. Some products are not eligible for the centralised procedure.

Mutually Recognised Products

26. A mutually recognised product is one that has been assessed and approved on a European level involving at least two EU MSs, i.e. evaluated via the mutual recognition or decentralised procedure.
27. The mutual recognition procedure (MRP) is a European authorisation route resulting in a mutually recognised product.
28. Mutual recognition must be used when a product is already authorised in at least one EU MS on a national basis and the MAH wishes to obtain an MA for the same product in at least one other EU MS.
29. The MS that has already authorised the product is known as the Reference MS (RMS). The RMS submits their evaluation of the product to the other MSs; known as a Concerned MSs (CMS). The CMS is asked to mutually recognise the MA of the RMS.
30. If the application is successful, the CMS will then issue an MA for that product permitting the marketing of that product in their country.
31. Please note if the UK acts as RMS this means the product was initially authorised in the UK on a national basis; therefore, once the MRP has been successfully completed, the authorisation type of the UK MA will change from 'National' to 'Mutually Recognised'.
32. The decentralised procedure (DCP) is a European authorisation route resulting in a mutually recognised product.
33. The difference between MRP and DCP is that a product must already be authorised in at least one MS on a national basis in order for MRP to be used. DCP may be used if the product is not authorised in any EU MS and a company wishes to

authorise it in several or all EU MSs, but only if the centralised procedure is not mandatory, or the company does not wish to use the centralised procedure (where it is optional), or the product is not eligible for the centralised procedure.

34. One of the proposed MSs will be asked by the MAH to act as the RMS. The RMS does the initial evaluation of the product and issues a draft assessment report including a list of unresolved issues. The CMS either agree with the RMS's evaluation or they ask further questions/raise objections.
35. If all the issues are resolved and the application is successful, each MS will then issue an MA for that product permitting it to be marketed in their country.

Legal Bases

36. Within these routes, there are several different legal bases upon which an application for an MA may be applied for, which reflects the type and content of the data submitted in support of the application.
37. The data and documents required in support of an application for an MA are set out in *Volumes 6a and 6b of the European Notice to Applicants* and in Annex I to Directive 2001/82/EC, as amended. Please note this does not apply to Exceptional MA (ExMA) or Marketing Authorisations for Parallel Import (MAPI), which are national only schemes that are covered in separate Chapters.
38. Some applications for an MA will be based on a full data package where all parts of the data requirements are supported using the MAH's proprietary data, or using bibliography, i.e. published data, or a mixture of both. These MAs are known as 'Full MAs'.
39. There are some circumstances when a reduced data package may be submitted in support of a Full MA; this usually occurs:
 - For applications for an MA for Minor Use, Minor Species (MUMS), or
 - When an applicant refers to one of their own already authorised UK veterinary medicines in support of an application to extend that MA. This will result in an Extension MA.
40. There are also some circumstances when specific data may be omitted from an application for an MA that is not considered a Full MA; this usually occurs when:
 - an applicant refers to data already submitted and assessed as part of a data package submitted in support of an application for another MA known as abridged applications; this will result in an 'abridged MA', or
 - an applicant submits a reduced data package in order to obtain an ExMA, or
 - when an applicant refers to an already authorised UK veterinary medicine in support of an application to obtain a MAPI.

CHAPTER 2

Full and Abridged Marketing Authorisations

Introduction

41. Some applications for an MA will be based on a full data package where all parts of the data requirements are supported using the MAH proprietary data, or using bibliography, i.e. published data, or a mixture of both. These MAs are known as 'Full MAs'. There are some circumstances when the data package provided in support of a Full MA may be reduced, and there are also some circumstances when specific data may be omitted from an application for an MA, which will result in an abridged MA.
42. Therefore, this chapter provides information on the submission and assessment of applications for full and abridged MAs.

Full MA

43. There are a number of different ways to obtain a Full MA based on the data package provided in support of the application.
 - An MA based on a full data package using the MAH's proprietary data.
 - An MA based on a full data package where all parts are addressed using bibliography, i.e. published data. This is referred to as a bibliographic MA, or an MA based on well-established use. The applicant must demonstrate the active substance has been used for at least ten years in the target species for the indications applied for.
 - An MA based on a full data package using a mixture of the MAH's proprietary data and bibliography.
 - An MA based on a reduced data package for Minor Use Minor Species (MUMS). Specific data may be omitted from the data package submitted in support of an application for a MUMS MA. Further information about MUMS applications is available on the EMA website: www.ema.europa.eu.
 - An MA based on a reduced data package for an Extension MA.

Extension MA

44. The area of extensions can be slightly confusing because, technically, an extension is considered to be a type of variation, which may result in the creation of a new stand-alone MA. The MAH may extend an existing MA in order to:
 - create a new stand-alone MA known as an Extension MA, or
 - vary an existing MA.

45. If the MAH wishes to retain the extension as a stand-alone MA the application will be dealt with as a 'new extension' resulting in the grant of a new MA called an Extension MA. In such cases the applicant cross-refers to the already authorised UK veterinary medicine, which is referred to as the 'parent' product, and submits additional data to support the extension.
46. If the applicant wishes to have the extension 'rolled back in', the application will be dealt with as a 'variation extension'; a new MA will not be granted at the end of the procedure; instead the existing 'parent' MA will be varied.
47. Upon submission of an application the MAH must state which option they wish to pursue.
48. Further information about extensions is available in Chapter 6.

Abridged MA

Informed Consent - 'Copycats'

49. One of the most common types of abridged application is the 'copycat'; this is an informal term used by the UK to describe an MA authorised on the basis of informed consent, which results in an MA known as a 'copycat'. In such cases the applicant cross-refers to specific parts of the data package for an already authorised UK veterinary medicine, which is referred to as the 'parent' product. For these applications, only a full Part I of the dossier needs to be submitted (including European tables of materials of human and animal origin). Apart from the product name, the product's authorisation number and, possibly, the MAH and pharmacovigilance systems (DDPS), all of the details of the proposed copycat are identical to the parent.
50. In order for a product to be authorised on the basis of informed consent, the MAH for the parent product must have given the VMD permission to refer to the data submitted in support of the parent product. If the MAH of the parent product is different from the MAH of the proposed copycat, a formal letter of access from the parent MAH is required; this should be submitted as part of the application package submitted in support of the copycat. If the MAH of the parent and copycat products are the same, a formal letter of access is not required.
51. A copycat may be authorised via a national application procedure, or via the mutual recognition or decentralised procedures. In order for the copycat product to be considered under MRP or DCP, the parent product must already be mutually recognised, i.e. authorised via MRP or DCP. The MS that acted as the RMS during the procedure to authorise the parent product will also act as the RMS during the procedure for the copycat product.

Generics

52. General information about generic MAs is available below; however, more detailed information about generics is provided in the CMDv Best Practice Guide entitled, 'Approach for processing generic applications', which can be found on the Co-ordination Group for Mutual Recognition and Decentralised procedures - veterinary

(CMDv) pages of the Heads of Medicines Agency (HMA) website at:
<http://www.hma.eu/159.html>

53. A generic MA arises when the applicant refers to the safety and efficacy aspects of a data package submitted in support of an already authorised veterinary medicine, which is referred to as the 'reference' product. Nevertheless, in addition to a full quality data package, the applicant would need to provide an environmental risk assessment for the product and a user risk assessment. The type of user risk assessment provided depends on the degree of similarity between the generic and reference products. For generics of injectable products the submission of injection site residues data are necessary, unless a biowaiver exempts the application from the need for residues studies. Applicants must demonstrate that the generic product is bioequivalent to the reference product, unless they are exempt from doing so under the bioequivalence guidelines. The reference product must have been authorised in accordance with the Directive for at least 10 years before the generic product can be placed on the market. For applications for generic products, which are based on reference products authorised after October 2005, the application can be submitted after eight years of authorisation, but the generic product cannot be marketed until the 10 year data protection period has expired.
54. In certain circumstances the data protection periods applicable to the reference product may be extended to 13 years. For products indicated for the treatment of bees and fish the protection period of the reference product is automatically 13 years.
55. The SPC of the generic product should follow the SPC of the reference product.
56. It should be noted that generics of biological products are not possible unless the Master Seed and production process are the same.

Hybrids

57. A hybrid MA follows the same principles as noted above for generic applications, but such applications are required under the following two scenarios:
 - the applicant is not able to demonstrate bioequivalence to the reference product through bioavailability studies, or
 - where bioequivalence can be demonstrated to the reference product, but the applicant wants to make changes, e.g. in the active substance(s), or changes to the therapeutic indications, strength or pharmaceutical form or to the route of administration.
58. An example of a hybrid MA is as follows: the reference product is indicated for use in cats and dogs and is administered orally. The applicant wants their product to also include cats and dogs, but wants an injectable product. The applicant refers to the reference product to cover some of the safety and efficacy data requirements, but produces their own data to support the change in the route of administration.

BioSimiliars

59. Where a biological product, which is similar to a reference biological product, does not meet the conditions in the definition of a generic product, owing to, in particular,

differences relating to raw materials or in a manufacturing processes of the biological product and the reference biological product, the results of appropriate pre-clinical tests or clinical tests relating to these conditions must be provided.

The Application Process

Submission and Validation

60. Applications should be submitted in accordance with the guidance provided in Chapter 8.
61. The data and documents required in support of an application for a Full or Abridged MA are set out in *Volumes 6a and 6b of the European Notice to Applicants* and in Annex 1 of Directive 2001/82/EC, as amended.
62. Applications are submitted to the VMD along with the appropriate data required to support the proposed MA. The data provided should be robust and are assessed on their merits in relation to the application. Other data or knowledge that the VMD might have regarding similarly authorised products can only be taken into account in very clear and defined circumstances relating to the submission of abridged applications.
63. All applications for MAs are subject to validation, i.e. a check of their validity prior to accepting them for assessment; guidance on how to submit a valid application is provided on the VMD website.
64. The onus is on the applicant to identify and submit all the necessary supporting data in their application package. If the application is incomplete it is likely to fail validation. **The applicant should declare any ongoing studies relevant to the application.**
65. All MAs are subject to the SPC and product literature requirements outlined in Chapter 7. However, for applications for products subject to the MRP or DCP, it is particularly important that the applicant considers the labelling requirements at the outset, because some MSs require more than one language to appear on the product labelling; therefore, as a guide, text layouts setting out the required information three times in English should be submitted with the application.

Assessment and Outcome

66. The procedures and timescales for dealing with an application for an MA via MRP or DCP are outlined in the *Best Practice Guides* available on the HMA website <http://www.hma.eu/159.html>. Further information about the procedures and timescales used for the assessment of applications for MAs dealt with on a national basis is provided on the VMD website under the Thematic Link – Pharmaceutical Industry.
67. Although there is an opportunity formally to ask several sets of questions during the application procedure, it is essential that the responses provided are comprehensive and all pertinent data are provided in order to expedite progression of the application.

68. For applications dealt with via MRP or DCP - if one or more of the CMSs consider the benefit:risk assessment to be unsatisfactory, the application may be referred to CMDv for further discussion. Further information about the referral process is available in a *Best Practice Guide* available on the HMA website www.hma.eu. In the decentralised procedure, should the RMS, after assessment, reach a negative benefit:risk conclusion, then the procedure ends. Appeals may only be made under national procedures.
69. For applications dealt with on a national basis - if the proposed outcome is to refuse the application, the applicant will be notified of this and given an opportunity to appeal against this decision before it is implemented. For further information please refer to VMGN 9 Guidance on Appeals against Regulatory Decisions, which is published on the VMD's website http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx
70. If the outcome is to approve the application, the applicant will be sent authorisation documentation, as follows:

Following Completion of an MRP Application - UK as RMS

- A letter;
- an updated memorandum document;
- an updated Control Test Appendix (CTA), if applicable, for biological products only;
- an updated SPC and product literature, and
- an updated Finished Product Specification (FPS), if applicable, for pharmaceutical products only.

Following Completion of all other Applications

- A certificate;
- a memorandum document;
- a CTA, for biological products only;
- an approved SPC and product literature, and
- an FPS, for pharmaceutical products only.

United Kingdom Public Assessment Report (UKPAR)

71. All products authorised after 30 October 2005 should have a public assessment report in accordance with legislation. The UKPAR is a summary of the assessment report drafted during the application procedure covering quality, human and environmental safety, and target animal safety and efficacy. Post authorisation assessments are also recorded, e.g. any variations or renewals conducted on an MA. The MAH has an opportunity to comment on the draft UKPAR before publication.
72. For nationally authorised products the UKPAR can be found on the Product Information Database on the VMD website. For mutually recognised products it is the responsibility of the MS acting as the RMS for the procedure to draft the report. Where the product is mutually recognised the public assessment report will appear on the VMD website only if the UK have acted as RMS. Where the UK has acted as CMS only the high level product details and SPC will be made available.

73. Veterinary medicines authorised via the centralised authorisation route will have a European Public Assessment Report (EPAR), which can be found on the EMA website.

Post Authorisation Steps

74. Full and abridged MAs are subject to the renewal requirements outlined in Chapter 5.
75. In order to make any changes to an MA, the MAH must submit a variation application to the VMD in accordance with the guidance provided in Chapter 6.

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CHAPTER 3

Exceptional Marketing Authorisations (ExMA)

Introduction

76. There are some circumstances when specific data may be omitted from an application; this can happen when an applicant submits a reduced data package in order to obtain an ExMA.
77. ExMAs may only be issued in exceptional circumstances and may only be obtained via a national procedure. The resulting ExMA may not be mutually recognised at a later date.
78. There are two types of ExMAs - Provisional and Limited.
79. It has been possible to obtain a **Provisional Marketing Authorisation (PMA)** for veterinary medicines in the UK for a number of years. These authorisations are applicable where there is no fully authorised veterinary medicine in the UK available to prevent or treat a particular condition. These authorisations are issued whilst the MAH continues to generate the full supporting data required to obtain a full MA. PMA's are usually applied for and issued in order to address an urgent situation, e.g. as a result of a new disease, or because the nature of an existing disease has changed. These authorisations are intended to exist only in the short term and are expired when the corresponding full MA is granted.
80. **Limited Marketing Authorisations (LMA)** were introduced as a new scheme in October 2009; this scheme does not apply to FULL applications otherwise submitted in accordance with EMA guidelines on data requirements relating to MUMS/Limited Markets. LMAs are intended to be used in the case of veterinary medicines which, by the nature of the indicated species or the nature of the condition they are preventing or treating, are not expected to be sold in vast quantities - so called limited market products. LMAs are intended to help fill existing therapeutic gaps in the UK. As a result of the costs involved in generating complete data packages, and the anticipated low level of returns on the sales of such products, it is unrealistic to expect MAHs to generate complete data packages for limited market products and therefore there is no obligation to do so. However, should an MAH wish to generate the necessary data and apply to convert an LMA to a full MA they may do so.
81. For PMAs and LMAs it is necessary for the applicant to demonstrate that the benefits of the product outweigh any risks, taking into account any data that may be missing from the supporting data package.
82. The benefit:risk balance presented by the applicant should take into account the alternatives to using the proposed product, e.g. withholding treatment, or treatment under the cascade. Treatment under the cascade has a number of disadvantages, e.g. a human medicine can be used, but the presentation (e.g. tablet strength, formulation) may be unsuitable for the bodyweight range of the intended veterinary target species; furthermore, a human medicine will not contain any specific recommendations on the veterinary use and the MAH is unlikely to be willing to provide advice in connection with use in animals. Another example would be using

an EU authorised veterinary medicine that, in most cases, will not be labelled in English, so advice on correct use will not be directly to hand.

Eligibility

83. ExMAs may be applied for in the case of any veterinary medicine that will fill a therapeutic gap in the UK. When considering whether or not a therapeutic gap exists in the UK, account will be taken of the veterinary medicines already holding a full MA in the UK. No account will be taken of medicines already in use via the cascade system, e.g. human medicines, or veterinary medicines authorised elsewhere in the EU, or made available through Schedule 6 of the VMR - Exemptions for Small Pet Animals, or products which hold a PMA or LMA (but it should be noted that cascade alternatives are taken into account when assessing the benefit risk balance of the product during a PMA or LMA procedure (refer to paragraph 82)).
84. The active substance(s) contained within products intended for use in a food species must have a Maximum Residue Limit (MRL) status in order to apply for an ExMA (refer to the Table of Allowed Substances in Commission Regulation 37/2010) available at http://ec.europa.eu/health/files/eudralex/vol-5/reg_2010_37/reg_2010_37_en.pdf.

Therapeutic Allergen Products

85. Therapeutic allergen products may qualify for consideration for an LMA. A case for establishing that the proposed product falls within the definition of limited markets should be presented with the application.
86. In some cases it is anticipated that the authorisation of bulk concentrated allergens will be appropriate. These may then be used to formulate dosage forms for individual animals on a case by case basis as extemporaneous preparations.
87. The inclusion of specific allergens in the application should be justified and its relevance to the clinical situation in UK should be explained.
88. All relevant data available at the time of making the submission of the application for an LMA should be included in the supporting data. As mentioned above, any gaps in the quality, safety and efficacy data must not be critical to the safety of the product and it must be possible to mitigate any risks to an acceptable level.
89. The allergenic active ingredients should be described in as much detail as possible and this should include specifications and control methods relating to identity and purity of the source material.
90. The production process for each allergen or group of allergens should be described step by step with a flow chart, with an indication of when aseptic precautions are introduced. Intermediate or bulk products in the process should be identified and the in-process controls should be described.

91. In certain cases, data obtained with a representative allergen product may be extrapolated to another, as long as a close relationship exists between their active components. It may be necessary to sub-divide some groups into smaller families and justification for this division should be provided.
92. Each family or subgroup of allergens must be described and tested separately.
93. Batch to batch consistency should be established by comparison with in-house reference preparations using a number of biological and analytical methods. Consistency of production must be documented on at least three production runs.
94. For stability data, the concept of the homologous groups may be applied and data obtained on one member of the family may be extrapolated within the same family. A shelf life longer than 12 months is only acceptable with stability studies obtained by immunological or equivalent methods that can demonstrate allergenic activity throughout the shelf life period.
95. The concept of the homologous groups may also be applied for the performance of clinical trials.
96. Measurement of total allergenic activity of individual batches of each allergen extract should be undertaken using validated immuno-assay methods.

Distribution Category

97. Any product granted an ExMA will be a Prescription Only Medicine (POM-V).
98. For PMAs, for at least the first 12 months, products will be POM-V with the possible exception of products for bees. Products will usually remain in this distribution category while they are authorised as a PMA; however, once the product has been marketed for at least 12 months with a high volume of sales, it may be possible for the product to be considered for Prescription Only Medicine - Veterinarian, Pharmacist, Suitably Qualified Person (POM-VPS) status if the product makes only preventative claims and has a good record in terms of Adverse Events (AE) and Suspected Lack of Efficacy (SLE). Any change to distribution category would have to be applied for by means of a variation with appropriate supporting data. Further information about variation procedures is available in Chapter 6.

The Application Process

Submission and Validation

99. Applicants are required to contact the VMD to organise a meeting with assessors prior to the submission of an application for an ExMA (see also paragraph 109). This provides an opportunity to discuss whether the dossier supporting the proposed application is likely to be sufficient to enable it to be progressed.
100. Applications should be submitted in accordance with the guidance provided in Chapter 8. In addition to these requirements, specific guidance in relation to applications for ExMAs is provided in the following paragraphs.

101. The data and documents required in support of an application for an ExMA should be presented in accordance with the structure for Full MA applications set out in *Volumes 6a and 6b of the European Notice to Applicants* and in Annex 1 of Directive 2001/82/EC, as amended. The applicant should also include expert reports and an overall benefit:risk assessment.
102. The applicant must complete all parts of the application form, which is a VMD-created document that is available on the VMD website.
103. In the covering letter accompanying the application, information should be provided demonstrating that the product will fill a therapeutic gap in the UK market.
104. In support of an application for an LMA, the case for establishing that the proposed product falls within the definition of limited markets should be presented. In terms of the definition of limited market reference can be made to the EMA paper “*EMA Guidance for Companies Requesting Classification as MUMS/Limited Markets*”, EMA/CVMP/370663/2009. Whilst this is an EMA document, the headings in the referenced template may be used as a basis to present to the VMD the case that the proposed product is intended for use in a limited market. If the template is used it should be sent to the VMD with the application, and should not be sent to the EMA. The template includes background information on the applicant and product profile of the VMP. It also requests information under the following headings:
- Target species.
 - Prevalence of the condition in the EU, including geographical distribution (although specific emphasis should be given to the UK situation).
 - Current and/or alternative approaches to therapy and available treatments.
 - Severity of the condition and the need for this medicinal product.
 - Potential zoonosis, if applicable.
 - If the product is intended for use in food producing animals - need for an MRL.
 - Is the product indicated for a disease that is subject to Community control measures?
 - Potential market size and return on investment.
 - Authorisation status.
105. All new ExMA applications are subject to validation. Further information about validation requirements is available on the VMD website.
106. The onus is on the applicant to identify and submit all the necessary supporting data in their application package. If the application is incomplete it is likely to fail

validation. The applicant should declare any ongoing studies relevant to the application.

107. Data gaps may exist in any section of the dossier, i.e. quality, safety and efficacy, but these must not be critical to the safety of the product and it must be possible to mitigate any risks to an acceptable level.
108. All relevant data available at the time of making the submission of the application for an ExMA should be included in the supporting data.
109. The following is not intended to be an exhaustive list, but, instead, is intended to illustrate the types of data gaps that might be acceptable, but it is important to emphasise these cannot be considered in isolation from any other data gaps. Instead the complete data package and any gaps must be considered and this information must be fed into the benefit:risk assessment. As noted in paragraph 99, applicants are expected to attend a pre-submission meeting with assessors of all disciplines in order to ensure that expectations of data requirements are understood; this meeting provides the opportunity for these requirements to be discussed in the context of the specific application.

Quality

- Antimicrobial preservative efficacy and broached vial studies have not been conducted, but the labels indicate the product should be used immediately following first opening.

Safety

- Skin and eye toxicity data on the formulation are not available, but a scientific evaluation can be made using available data on the active substance(s) and excipients, such as Material Safety Data Sheets (MSDS), published toxicity profiles (which may need to be purchased), or published literature, to predict the potential for skin and eye irritation and skin sensitisation and propose appropriate user warnings. The labels carry the agreed user warnings.
- Residue depletion studies are not available, but a scientific evaluation can be made using the pharmacokinetic data in the target species and the data in the MRL summary report to predict the expected depletion of residues and propose appropriate withdrawal periods or support “standard withdrawal periods” (as defined in legislation) that include additional “uncertainty factors” (usually in the form of additional days) to address the absence of data. The labels clearly state the agreed withdrawal period and that residue studies have not been performed and indicate what safety margin (uncertainty factor) has been applied, where applicable.

Efficacy

- Pharmacokinetics, pharmacodynamics: new studies using the proposed formulation in the target species are not available but the PK/PD profile of the active substance is well described in published peer reviewed papers; interspecies extrapolation may be acceptable if physiologically justified.
- Safety: target species tolerance data using the proposed formulation are not available but peer reviewed papers or published toxicology profiles are

available which characterise the margin of safety in the target species and the proposed product contains excipients with well known safety profiles, and field safety data for the final formulation are available for the proposed dose.

- Field trial data are not available, but sufficient relevant data generated in laboratory studies in the target species (using the final formulation to be marketed) are available to indicate that the product is likely to work and to indicate the dose regimen selected is appropriate. The labels indicate that field trials have not been undertaken.

110. Once the application has passed validation it will proceed into the assessment phase.

Assessment and Outcome

111. The application will be assessed and processed in a similar way, and usually to the same timescale as an application for a Full MA. Further information about the timescales used for a Full MA is available on the VMD website.

112. In the case of an application for a PMA, where the product is intended to address an urgent situation, the assessment process will be accelerated as far as is reasonably possible taking account of available resources and other commitments.

113. Although there is an opportunity formally to ask several sets of questions during the application procedure, it is essential that the responses provided are comprehensive and all pertinent data are provided in order to expedite progression of the application.

114. If the proposed outcome is to refuse the application, the MAH will be notified of this and given an opportunity to appeal against this decision before it is implemented. For further information please refer to VMGN 9 Guidance on Appeals against Regulatory Decisions, which is published on the VMD's website http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

115. If the outcome is to approve the application, the applicant will be sent authorisation documentation, which is comprised of:

- A certificate;
- a memorandum document;
- a CTA, for biological products only;
- an approved SPC and product literature; and
- an FPS, for pharmaceutical products only.

116. The authorisation will be subject to a number of conditions, the nature of which will depend on the type of authorisation, the product concerned and the supporting data provided. However, all authorisations will specify the need to submit Periodic Safety Update Reports (PSUR) and the timing of this.

117. The following are examples of the type of conditions which could be proposed:

- requirement to submit renewal application(s) and the timing of this and the supporting data to be supplied;
- requirement to establish a structured programme for the collection and investigation of AE(s);
- requirement to establish an active programme for monitoring safety and/or efficacy in use;
- controlled distribution, in some circumstances additional controls through Animal Health (animalhealth.defra.gov.uk) or named veterinary surgeons might be appropriate.

118. In the case of **PMAs** there will be a condition to complete and/or conduct trials in order to finalise a dossier suitable for submission for a full MA and to submit this dossier to the VMD. A time period, usually of no more than three years, will be set for this.
119. In the case of **LMAs** there will be a condition setting out that if the company elects to conduct further studies, the results of these studies must be submitted to the VMD whether the results are favourable or not. Additional data should be submitted in the form of a variation application.

Labelling

120. In addition to the normal requirements for labelling for veterinary medicines, as outlined in Chapter 7, products subject to an ExMA are required to carry the following information on their product literature:
- A clear statement that the product does not have a full MA and to highlight the area of “weakness”. For example, “This is a Limited Marketing Authorisation. A full set of supporting efficacy data is not available for this product”.
 - The statement “All adverse events and any suspected lack of efficacy should be reported to [*insert company pharmacovigilance contact number and address*]”.
 - The statement “Further information on this product and its supporting data can be found on the product information database available on the VMD website”.
121. The first of these statements should, wherever possible, appear on the immediate packaging. Where this is not possible this statement, together with the other statements, should appear on the outer packaging, or package leaflet.

United Kingdom Public Assessment Report (UKPAR)

122. As set out in paragraph 71 above, a public assessment report will be made available on the VMD website. In addition to the usual format for UKPAR, the report for an ExMA may set out where limited data has been submitted. This will be updated upon approval of variations.

Post Authorisation Steps

Reassessment of an ExMA

123. ExMAs will be subject to an annual reassessment by the VMD following grant of the initial authorisation. This reassessment will examine all of the relevant information available to the VMD, including PSUR, and will be completed within 30 days of the 'reassessment date'. The purpose of the assessment is to confirm that the benefit:risk balance remains favourable. Where this is not the case the authorisation may be suspended or revoked and the MAH will be advised of this accordingly.
124. In addition, for **PMAs**, the VMD will also check to see if a product with a Full MA for the same species and identical indications has been authorised in the UK. Where this is the case the PMA will be expired and the MAH will be advised of this accordingly.
125. The VMD must take due account that other companies may be generating data to support a Full MA for the relevant species/condition covered by a **LMA**. Where a full MA is granted in the UK for a product that will treat the exact same condition in the same species as the LMA, the MAH of the LMA will be given immediate notice of the intended expiry of their authorisation as follows:
- Where the active substance is the same, the authorisation will be expired one year from the date of grant of the relevant UK full MA.
 - Where the active substance is different, the authorisation will be expired five years from the date of grant of the relevant UK full MA.
126. MAHs will only be required to submit renewal applications where this is specified as a condition on the initial authorisation. In these cases, the timing of the renewal and the supporting data to be supplied will also be specified. In many cases renewal applications will not be required.

Changes to an ExMA

127. In order to make any changes to an ExMA, the MAH must submit a variation application to the VMD in accordance with the guidance provided in Chapter 6.

CHAPTER 4

Marketing Authorisations for Parallel Imports (MAPI)

Introduction

128. A parallel import arises when a veterinary medicine is authorised in the UK and a product, that is identical (for food-producing species), or therapeutically the same (non-food producing species), is authorised in at least one other MS of the EU, and the product is bought from wholesalers in one MS and imported into the UK for distribution. The imported product must be subject to a valid MAPI.
129. The UK authorised product upon which the MAPI is based is known as the 'parent'; this parent may be nationally authorised, or mutually recognised. The procedure for obtaining a MAPI is slightly different depending on the authorisation route of the parent.
130. A MAPI based on a nationally authorised parent product may cover a product imported from one MS only; however, a MAPI based on a mutually recognised product may cover a product imported from more than one MS.
131. A MAPI may only be obtained via a national procedure; however, the VMD will liaise with the MS from which the product is being imported to obtain specific information to aid the authorisation process.
132. Once a MAPI has been granted, it may not be mutually recognised at a later date.

Eligibility

133. The product to be imported into the UK, i.e. the MAPI product, must be a VMP authorised in accordance with Directive 2001/82/EC, as amended, in the MS from which the product is to be imported. This will always be the case when the parent product is mutually recognised, but may not always be the case if the parent product is nationally authorised.
134. The MAH of the MAPI product must be established within the Community as outlined in Chapter 1. In addition to this, the MAH must:
- be the holder, or have a contract with a holder, of a suitable UK Wholesale Dealers' Authorisations (WDA); and
 - be the holder, or have a contract with a holder, of a suitable Manufacturer's Authorisation (ManA).

Distribution Category

135. The distribution category of the MAPI product will be the same as the distribution category of the parent product.

The Application Process

Submission and Validation

136. Applications should be submitted in accordance with the guidance provided in Chapter 8. In addition to these requirements, specific guidance in relation to applications for MAPI is provided in the following paragraphs.
137. The data and documents required in support of an application for a MAPI are listed in the application form, which is available on the VMD website.
138. The applicant must complete all parts of the application form.
139. For MAPIs based on a nationally authorised parent product; separate applications must be submitted for each MS that the MAPI product is to be imported from.
140. For MAPIs based on a mutually recognised parent product; the name of each MS from which the MAPI product is to be imported should be included on the same application form. If granted, the import of the MAPI product from each MS will be covered by the authorisation. Additional MSs may be added to the authorisation at a later date; this may be done by way of a variation application. Further information about national variation procedures is available in Chapter 7.
141. The applicant should provide a detailed description of the pharmacovigilance system, and where appropriate, the risk management system that will be put in place by the MAH. Although a MAPI is granted in response to a special abbreviated application, the MAPI holder should ensure that they can fully comply with the requirements set out in VMGN 11 Pharmacovigilance Guidance on Adverse Events, which is published on the VMD's website http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx.

In particular a MAPI holder must:

- Establish systems specific to each product to ensure that any batch recalls or safety issues in the country of export are identified and reported to the VMD.
 - Notify the VMD immediately of any events or developments in the country or countries from which the product is imported which may affect the safety, quality or efficacy of the product, or the terms of the MA, including:
 - any variations to the authorisation in that country;
 - any recalls of batches;
 - any revocation or suspension of the authorisation; and
 - any information available to the importer concerning AEs or other factors which could affect safety in use.
142. If there is an impact on a MAPI from an AE involving a similar product, the VMD will inform the MAPI holder of any risk to human or animal health or the environment which has come to their attention. Likewise, the VMD may inform other MAHs of any risk to human or animal health or the environment which has been identified

through an AE involving a MAPI product. The VMD may notify the parent company of an AE involving a MAPI product.

143. The applicant must submit a draft SPC with their application; the SPC should be based on the SPC of the parent product, which will be available on the VMD website in the product information database.
144. A detailed description of the arrangements to be used for re-labelling the MAPI product will be required. This information should include:
 - the site of operations;
 - the name and qualifications of the person responsible for supervising the operations;
 - if re-labelling in the UK, particulars of the ManA;
 - if re-labelling outside the UK, a copy of the ManA for each site concerned.
145. All MAPI applications are subject to validation. Further information about the validation process is available on the VMD website.
146. The onus is on the MAH to identify and submit all the necessary supporting data in their application package. If the application is incomplete it is likely to fail validation.
147. Once the application has passed validation it will proceed into the assessment phase.

Assessment and Outcome

148. The application will be assessed and processed in accordance with the timescales used for MAPI applications based on whether the parent product is nationally authorised or mutually recognised. Further information about the procedures and timescales for dealing with applications for MAPI is available on the VMD website.
149. The VMD will liaise with the MS from which the product is being imported to obtain specific information to aid the authorisation process. The timescales for assessing the application will be suspended pending receipt of the information requested, which can take a while in most cases, because other MSs can be slow to respond.
150. It is not necessary for the parent and MAPI product to be manufactured by the same company, although the products should be therapeutically the same, unless justification can be provided to explain any possible differences. In cases where the information is not readily known to the importer, i.e. proposed MAPI holder, the VMD will assess the application on the basis of the details supplied. In order to ensure that the withdrawal period is appropriate, it is necessary to establish the identical nature of the formulation for pharmaceutical products authorised for food-producing species. In some cases the VMD may have to rely on information from other MSs to verify the identical nature or therapeutic equivalence of the products.
151. Although there is an opportunity to formally ask several sets of questions during the application procedure, it is essential that the responses provided are comprehensive and all pertinent data are provided in order to expedite progression of the application.

152. If the proposed outcome is to refuse the application, the MAH will be notified of this and given an opportunity to appeal against this decision before it is implemented.
153. If the outcome is to approve the application, the MAH will be sent authorisation documentation, which is comprised of:
- a certificate;
 - a memorandum document;
 - a CTA, for biological products only;
 - an approved SPC and product literature, and
 - an FPS, for pharmaceutical products only.

Summary of Product Characteristics (SPC) and Labelling

154. MAPI products are subject to the normal requirements for SPC and labelling for veterinary medicines as outlined in Chapter 7. Apart from the product's authorisation number, the MAH and, possibly, the product name, all of the details of the proposed MAPI should be identical to the parent.
155. The label should also include the original manufacturer's batch number and expiry date.

United Kingdom Public Assessment Report (UKPAR)

156. There will be no UKPAR for MAPI products due to the lack of available data. High level product details and the SPC will be available on the VMD website.

Post Authorisation Steps

157. Unless otherwise stated, MAPI products are subject to the same renewal requirements and variation procedures as Full MAs as outlined in Chapters 5 and 6 respectively.

CHAPTER 5

Renewal of a Marketing Authorisation

Introduction

158. An MA is valid for five years following grant of the initial MA. After this time the MA must be renewed in order for it to continue to be authorised. If an MA is not renewed by the renewal date it will cease to be valid.
159. The VMD will endeavour to send a reminder letter to the MAH of nationally and mutually recognised MAs, but these are sent as a courtesy and it remains the responsibility of the MAH to apply for renewal at the appropriate time.

Changes to an MA

160. Changes to an MA that affect the SPC, labels and leaflet cannot be made during the renewal process; in order to ensure an MA is as up-to-date as possible; any changes to the MA must be made by way of a variation(s), which must be submitted and approved prior to the submission of the renewal application. Therefore, it is the applicant's responsibility to ensure that this is done in time for the renewal to be submitted and approved before the MA ceases to be valid.
161. If any changes are identified during the renewal procedure, the renewal may be granted subject to a condition(s), i.e. the applicant may be asked to submit a variation following the conclusion of the renewal procedure in order to change the MA accordingly, which may be charged for and processed as per normal procedures.
162. Please note that a renewal application will not be accepted while the MA is subject to on-going variation procedures, and variation applications will not be accepted while the MA is subject to a current renewal procedure.

The Application Process

Submission and Validation

163. Applications should be submitted in accordance with the guidance provided in Chapter 8.
164. For mutually recognised MAs, a renewal application should be submitted to the RMS and CMSs at least six months prior to the date of renewal.
165. The applicant must complete all parts of the application form, which is available on the VMD website.
166. The data and documents required in support of an application for a renewal are set out in *Volume 6c of the European Notice to Applicants*.

167. For nationally authorised MAs, a renewal application should be submitted to the VMD at least nine months prior to the date of renewal.
168. The applicant must complete all parts of the application form, which is available on the VMD website.
169. A list of the data and documents required in support of an application for renewal of a nationally authorised MA is available on the VMD website.
170. All renewal applications are subject to validation; guidance on how to submit a valid application is provided on the VMD website.
171. Further information about the criteria for submitting SPC and product literature is provided in Chapter 7.
172. The onus is on the MAH to identify and submit all the necessary supporting data in their application package. If the application is incomplete it is likely to fail validation.
173. Once the application is deemed valid it will proceed into the assessment phase.

Assessment and Outcome

174. The procedures and timescales for dealing with the renewal of a mutually recognised product are outlined in the *Best Practice Guides* available on the HMA website <http://www.hma.eu/159.html>. Further information about the procedures and timescales used for the assessment of applications dealt with on a national basis is provided on the VMD website www.vmd.defra.gov.uk.
175. For applications dealt with via the MRP – if one or more MSs consider the benefit:risk assessment to be unsatisfactory, the application may be referred to CMDv for further discussion. Further information about the referral process is available in a *Best Practice Guide* available on the HMA website.
176. For applications dealt with on a national basis - if the proposed outcome is to refuse the application, the MAH will be notified of this and given an opportunity to discuss this with the VMD before the decision is implemented.
177. If the outcome is to approve the application, the MAH will be sent authorisation documentation, which is comprised of:
- a renewal certificate;
 - an updated memorandum document;
 - an updated CTA, if applicable, for biological products only;
 - an updated SPC and product literature, if applicable, and
 - an FPS, if applicable, for pharmaceutical products only.
178. Once renewed the MA will remain valid indefinitely unless the VMD considers that an additional renewal is justified on the grounds of pharmacovigilance five years after the first renewal (this may include products that have not been marketed for all or part of that time), or unless the MA is revoked or expired.

179. For products which have been mutually recognised or national products which may subsequently go through the mutual recognition process, the MAH may be required to submit further renewals even if the authorisation has an unlimited life in the UK. This is because the authorisations issued in other MSs are subject to the same legislation and, consequently, require at least one renewal. In such cases the RMS has the responsibility for managing the renewal procedure.

United Kingdom Public Assessment Report (UKPAR)

180. After a renewal has been granted, the UKPAR will be updated to reflect the change. Primarily this will involve recording the renewal in the Post Authorisation Assessment document. This will only be applicable to products that were issued after 30 October 2005.

WITHDRAWN AS OUT OF DATE

CHAPTER 6

Variation of a Marketing Authorisation

Introduction

181. A variation is a change made to an MA and involves changes to both the formal documentation and underlying data submitted in support of the MA.
182. Commission Regulation 1234/2008/EC sets out the procedures for handling variations; this was implemented in respect of mutually recognised and centrally authorised MAs on 1 January 2010. MSs will not be required to implement the new procedures to nationally authorised MAs until the EC amends Regulation 1234/2008.
183. Commission Regulation 712/2012/EC introduced a number of changes that come into force on 2nd November 2012. These changes concern the Commission's decision times associated with centrally authorised products; and the process for submitting unforeseen variation requests. Extending the scope of the variations regulation to include products authorised on a national only basis comes into force on 4th August 2013. . However, the VMD implemented the new procedures on 1 October 2011 ahead of this deadline in order to harmonise the variation procedures used in the UK.

General Information

Homeopathic Remedies

184. For the purposes of the VMR, a registered homeopathic remedy is a VMP and is subject to the same variation procedures as those applicable to a nationally authorised MA.
185. For further information please refer to VMGN 7 Guidance on the Homeopathic Registration Scheme, which is published on the VMD's website http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

Biological Veterinary Medicinal Product

186. A biological VMP is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physicochemical-biological testing, together with the production process and its control. Starting materials, the production process and all controls (starting material, in process and final product) have to be detailed.
187. The following shall be considered as a biological VMP:
- Immunological VMP (IVMP).
 - VMP derived from blood and plasma.
 - VMP falling within the scope of Part A of the Annex to Regulation (EEC) No 2309/93.

188. An IVMP is a VMP administered to animals in order to produce active or passive immunity or to diagnose the state of immunity to desensitize against allergens or to provide an effect based on interaction of antigens with specific antibodies.

Urgent Safety Restrictions

189. In the event of risk to public health, animal health or the environment, an MAH may impose urgent safety restrictions on a VMP after giving prior notice to the VMD in writing. In this case the MAH must inform the VMD of the proposed restrictions. If the VMD does not notify the MAH of any objections within 24 hours, the urgent safety restrictions may be introduced and an application for a variation must be submitted to the VMD within the following 15 days. All correspondence should be directed to a member of the General Assessment team.

Pharmacovigilance

190. Where variations involve changes to the pharmacovigilance system, including the detailed description of the pharmacovigilance system (DDPS), further information is available in the clarification paper published on the VMD website.

Variation Types

191. Variations are categorised as Type IA, Type IB, Type II or Extension. This classification reflects an increasing level of complexity involved in the assessment of the proposed change.
192. The list of changes categorised as Type IA, IB and II variations, together with conditions and data requirements, where appropriate, can be found in the current version of the EC's *Notice to Applicants 'classification guideline'*, which is available on the Commission website at: <http://ec.europa.eu>.
193. A list of changes categorised as Extensions is set out in Annex 1 of Commission Regulation 1234/2008/EC, as amended by Regulation 712/2012/EC.

Type IA

194. Minor variation, which has minimal or no impact on the safety, quality or efficacy of a product. Examples of Type IA changes are listed in Annex II of the Regulations and a complete list can be found in the classification guideline. Type IA variations are split into two sub-types:
- Type IA - annual reports: Notification of a change(s) must be made within 12 months of the change being implemented (which is defined as the date on which the Qualified Person (QP) released the first batch of product to which the change had been applied).
 - Type IA_{IN} - immediate notification: Notification of a change(s) must be made immediately after the change has been implemented.

Type IB

195. Minor variation, which is neither a Type IA nor a Type II nor an Extension; therefore, it is considered to be a Type IB variation by default. A list of some changes that are classified as Type IB can be found in the classification guideline.

Type II

196. Major variation that is not an extension, which potentially has a significant impact on the safety, quality and efficacy of a product. Examples of Type II changes are listed in Annex II of the Regulations and a list can be found in the classification guideline. Unforeseen variations may also be re-categorised from a Type IB to a Type II - please see below.

Extensions

197. A variation, which is listed in Annex I of the Commission Regulations.
198. An MAH may 'extend' an MA in order to:
- create a new stand-alone MA ('new extension'), or
 - change an existing MA ('variation extension', i.e. rolled back in).
199. Upon submission of an application the MAH must state which option they wish to pursue. If the MAH wishes to retain the extension as a stand-alone MA the application will be dealt with as a 'new extension'. The 'new extension' will be dealt with in accordance with new MA application procedures and timescales resulting in a new MA. A 'new extension' may not be submitted as part of a grouped variation (see Variation Applications).
200. If the applicant wishes to have the extension 'rolled back in', the application will be dealt with as a 'variation extension'; however, the 'variation extension' will be dealt with in accordance with new MA procedures and timescales, but a new MA will not be granted at the end of the procedure; instead the existing MA will be varied. A 'variation Extension' may be included as part of a grouped variation (see Variation Applications).
201. An example of an extension is the addition of a food-producing species. Product A is for use in cattle. The MAH decides to extend this MA to include sheep; they can either apply to create a new stand-alone MA, or vary the existing MA. If they choose to create a stand-alone MA, this will result in two products - product A for cattle and product B for cattle and sheep. If they choose to vary the existing MA, this will result in one product - product A for use in cattle and sheep.
202. A 'new-extension' may be progressed via a national application procedure, or via the MRP or DCP. In order for the extension to be considered under MRP or DCP, the parent product must already be mutually recognised, i.e. authorised via MRP or DCP. The MS that acted as the RMS during the procedure to authorise the parent product will also act as the RMS during the procedure for the extension.
203. A 'variation-extension' may be progressed via national application procedures for nationally authorised products, or via DCP for mutually recognised products.

Unforeseen Variations

204. Variations, that are not listed in the classification guideline and do not fall into the classifications listed in Annex II of the Commission Regulations, so called 'unforeseen variations', are by default Type IB. However, the applicant may request the VMD or CMDv to make a recommendation on the classification of an unforeseen variation or request for an application to be considered as a Type II upon submission. To ensure greater consistency across the European network, any unforeseen variation request received by the VMD will automatically be referred to CMDv for consideration. The VMD may also re-categorise an unforeseen variation as a Type II if they consider that it will have a significant impact on the quality, safety or efficacy of the VMP concerned. Applicants are encouraged to contact the VMD, prior to submission, in cases of unforeseen variations.

Additional Categories

205. A list of unforeseen variations, together with conditions and data requirements, that the VMD considers to be classified as Type IB for variations that are dealt with on a national basis only, is available on the VMD website. Therefore, the VMD does not need to be contacted prior to submission of these variations.
206. For variations relating to a 'change of legal entity of an MAH', a company merger or takeover may involve changes in the pharmacovigilance system and to the DDPS relating to the currently authorised MA(s). Consequently any variation under this category should be accompanied by a variation application to replace or change an existing DDPS, or an explanation as to why no change or variation is necessary, if appropriate. Further information about variations involving changes to the pharmacovigilance system is available in the clarification paper published on the VMD website.

Variations to MAs authorised on the basis of informed consent, i.e. 'Copycat' MAs

207. For variations to copycat MAs, where the same change has already been assessed for the parent product, the VMD will accept an unforeseen Type IB variation under the relevant category. This applies if the variation to the parent product was a Type IB, Type II, or an extension variation, and provided that no additional changes have been made solely to the copycat MA between authorisation and submission of the variation and that the supporting data package is identical. Therefore, a Type IB fee will apply and the variation will be dealt with in accordance with a Type IB timetable and procedures.
208. However, if between authorisation of the copycat and the submission of the variation, the copycat MA has been varied independently in such a way that the copycat MA has become different from the parent product, then the requested copycat variation will be dealt with in its own right in accordance with the variation type/category being applied for.
209. Where a parent authorisation has been varied using a Type IA procedure, a Type IA fee and timetable will apply to any copycat authorisation that requires the same change.

Harmonisation Variations

210. A harmonisation variation is a simplified procedure for harmonising the SPC and product literature of nationally authorised products (identical in terms of its formulation, packaging and manufacture in the UK and Ireland), so that products can be marketed using the same labels and, if applicable, leaflets in both countries.
211. Harmonisation variations are outside the scope of the new variation procedures. These variations are not intended to update the SPC and/or product literature, but to simply harmonise them, so if any changes to parts of the SPC require data to be assessed to bring them into line in the two countries then this will be dealt with by means of a separate variation to the relevant authority. The harmonisation variation cannot be progressed until all other applications have been completed on that product.
212. Harmonisation variations run on a 60-day clock, and the clock may start/stop a number of times during this period whilst the two countries discuss any issues and/or seek further information from the MAH, if required. Further information about harmonisation variations is available in the clarification paper published on the VMD website.

Change of Legal/Distribution Category

213. Changing the legal category (also known as distribution category) of a product is considered to be a Type II variation, which will be dealt with on a national basis regardless of the scope of a product i.e. mutually recognised or nationally authorised. In the case of centrally authorised products in the case of changes from POM-V to POM-VPS, or vice versa a national variation should be submitted to the VMD. Therefore, in order to change a product's legal category, a MAH should submit the appropriate application form and supporting data to the VMD in accordance with national variation procedures. It should be noted that change of legal category variations will usually be considered by the Veterinary Products Committee (VPC).

Non-Variations

214. The communication of new information, which does not affect the terms of the authorisation, is considered to be advice to the VMD. Such advice does not require prior approval from the VMD and it does not attract a fee.
215. Changes to the text of product literature (including its font and layout) may only be made as a variation to the authorisation. However, changes to the labelling that have no effect on the authorised text and that have no effect on the legally required statements and warnings, or their legibility, may be made without the need for a variation. For example, a change to a barcode or a company logo would not necessitate a variation. However, if these changes resulted in text being moved from the inner packaging to the outer packaging or required the inclusion of a package leaflet, or resulted in the change of font size to allow for a new logo, a formal variation would be necessary.
216. In order to communicate a 'non-variation', please contact a member of the General Assessment team.

Variation Applications

217. A variation application should be submitted for each change per product, i.e. one change to one MA = one variation; however, there are exceptions to this rule, i.e. grouped and work-sharing variations.
218. It should be noted that an MA may include all the different strengths and pharmaceutical forms of that product; therefore, a single variation involves one change to one MA, or one change to several related MAs.
219. A grouped variation is handled in the same way as the respective application type for the highest ranking variation included in the group, e.g. a grouped variation involving Type IB and Type II changes will be handled in accordance with the procedures and timescales of a Type II variation.
220. A work-share variation is handled in accordance with the procedures and timescales used for Type II variations.

GROUPED VARIATIONS

Type IA (one application form)

221. A number of Type IA changes to the terms of one or more MAs, held by the same MAH, may be applied for under cover of a single variation application, e.g.
- One change to several MAs.
 - Several changes to several MAs; the same changes apply to each product.
 - Several changes to one MA.
222. All MAs involved in a Type IA led grouped variation do not need to be related, but they must be held by the same MAH.

Type IB/II/Extension (one application form)

223. A number of changes to the terms of one or more MAs may be applied for under cover of a single variation application, e.g.
- Several changes to one MA
 - Several changes to several related MAs.
224. All MAs involved in a Type IB/II/Extension led grouped variation must be related, i.e. different strengths and pharmaceutical forms of the same product and must be held by the same MAH; this is not the case for variations dealt with on an administrative basis (see Administrative Variations).
225. At least one of the changes must be a Type IB, II or an Extension. The variations concerned must also fall within one of the cases listed in Annex III of Commission Regulation 1234/2008/EC, or, if they do not fall within one of the cases listed, the MAH should consult the VMD who must agree to progress the variation as a 'group'. In these cases, the MAH should contact a member of the General Assessment team.

226. A grouped variation will run on the longest timetable, e.g. if the variation includes a Type IA change, Type IB change, Type II change and an Extension, the variation will run in accordance with an Extension timetable. **Please note an Extension may only be included in a grouped variation if the applicant intends to retain the change as part of the original MA, i.e. not keep the Extension as a stand-alone MA.**
227. Applications involving Type II changes must be accompanied by an addendum to, or updating of, existing expert reports to take account of the variation(s) applied for.
228. Fees - each change per product is counted as a 'change'; therefore, if you are applying for three changes to six products these count as 18 changes for fee purposes.

Grouped Variations - Multiple Application Forms

229. A single change being made to the terms of several unrelated MAs will be applied for as separate applications (where the products are not different strengths or pharmaceutical forms of the same product). These can be considered a 'grouped' variation for fee purposes.

'Same' MAH - Definition

230. In the UK an MAH is identifiable by their unique company number, which forms the first part of a product's Vm number; if the product submitted as part of a group or workshare variation have different company numbers, but you believe them to belong to the same MAH, please provide justification for this in your covering letter.

WORK-SHARING VARIATIONS

231. The facility to work-share variations for national MAs was introduced on 4th August 2013. Therefore, it is now possible to operate work-share variations in terms of sharing assessment between MSs, so applicants can now benefit from the ability to submit several changes for a series of unrelated products, or to the same change for unrelated products, in a single procedure, i.e. one or more changes to the terms of several MAs, held by the same MAH, may be applied for under cover of a single variation application, e.g.

- One change to several products.
- Several changes to several products; the same changes apply to each product.

Where several changes are being made, this group should be covered by one of the cases listed in Annex III of the Commission Regulations.

232. The application may only include Type IB and/or Type II changes. It may also include Type IA changes that are consequential to the other changes being made. A work-sharing application cannot include an Extension variation.
233. A work-share variation involving the UK only will run on a national Type II timetable; a work-share variation involving other MSs will run on an EU Type II timetable. The timetable used will be the same regardless of the types of changes involved, e.g. if all changes are Type IB, the variation will still run on a Type II timetable.

234. Fees - each change per product is counted as a 'change'; therefore, if you are applying for three changes to six products these count as 18 changes for fee purposes.

ADMINISTRATIVE VARIATIONS

235. Applications involving administrative changes only, as defined below, will be dealt with in accordance with national administrative variation procedures. Administrative changes include the following:

- Type IA - change of name and/or address of MAH (same legal entity). As a consequence to a change in the name of MAH, changes to the name only of the manufacturer and/or assembler of active substance and to the name only of the finished product manufacturer will also be considered administrative when submitted as part of the same grouped variation. Each change will be charged for accordingly.
- Type IB – change of legal entity of MAH and change of distributor details (unforeseen variations). Please note these changes will be dealt with on a national basis regardless of the scope of the MA, i.e. mutually recognised or nationally authorised.
- If the name and/or address of a distributor changes as a consequence of a change of legal entity, or a change to the name and/or address of MAH (same legal entity), the first distributor change will be charged for accordingly, but all subsequent consequential distributor changes will be processed free of charge. In order to achieve this, applicants should submit the distributor change as part of a grouped variation involving the change of MAH, and within six months of the original distributor change.
- Other - in exceptional circumstances a number of other changes may be dealt with on an administrative basis, e.g. post-Committee for Medicinal Products for Veterinary Use (CVMP) referral changes; in these cases the variation will run in accordance with an administrative timetable.

236. If administrative changes are submitted as part of a single application, or part of a grouped application involving other administrative changes only, they will be dealt with in accordance with an administrative variation timetable which is available on the VMD website. The MAs included in an administrative grouped variation does not need to be related, but they must be held by the same MAH. Fees will be charged for in accordance with the highest ranking change, e.g. if the highest ranking change is a Type IB variation, the fee will be as per the charge for a single or Type IB led grouped variation.

237. A single administrative variation, or an administrative grouped variation involving up to nine changes, will be dealt with in accordance with a 30-day timetable; however, an administrative grouped variation involving more than nine changes will be dealt with in accordance with an extended 60-day timetable. It should be noted that an administrative variation will be subject to a 10-day validation period; however, for applications involving administrative Type IA changes only, a separate validation period will not apply.

The Application Process

Submission and Validation

238. Applications should be submitted in accordance with the guidance provided in Chapter 8.
239. The data and documents required in support of an application for a variation dealt with via national or mutual recognition variation procedures are set out in the classification guideline. A list of the data and documents required in support of an application for an unforeseen variation, dealt with on a national basis only, is available on the VMD website.
240. All variation applications are subject to validation; guidance on how to submit a valid application is available on the VMD website.
241. It should be noted that an 'all or nothing' approach will be adopted with regard to grouped or work-sharing variations at validation; therefore, an application will only progress once all aspects of the application package are deemed satisfactory.
242. Applications involving Type IA changes only are not subject to a separate validation; they will proceed straight into the checking phase of the application procedure upon receipt. A fee is therefore charged whether the variation is approved or refused; there is no opportunity to defer the assessment or request additional data/information.
243. Further information about the criteria for submitting SPC and product literature is provided in Chapter 7.
244. The onus is on the applicant to identify and submit all the necessary supporting data in their application package. If the application is incomplete it is likely to fail validation.
245. Once the application is deemed valid it will progress into the assessment phase.

Assessment and Outcome

246. The procedures and timescales for dealing with a variation application via the mutual recognition variation procedures are outlined in the *Best Practice Guides* available on the HMA website <http://www.hma.eu/159.html>.
247. The procedures and timescales for dealing with a variation application via the national variation procedures are available on the VMD website. Please note national variation procedures are applicable to nationally authorised products, i.e. MA authorised on a national basis, or changes dealt with on a national basis regardless of the scope of the MA (refer to paragraph 205 - unforeseen variations dealt with on a national basis).
248. Applicants may withdraw an entire application, or one or more of the changes included as part of a grouped or work-sharing variation.
249. If the application is refused, i.e. all changes are rejected, the applicant will be notified of this at the end of the assessment period.
250. Where a notification concerning one or several Type IA variations is rejected, the MAH shall cease to apply the concerned variation(s) immediately. In some cases this may have the consequence that the MAH must cease to apply already implemented changes. Within 14 days of notification of rejection of a Type IA variation, the MAH must inform a member of the General Assessment team that they have ceased to apply the change(s) and, if appropriate, should re-submit a variation for the change(s) under the correct classification with the appropriate supporting data.
251. If the outcome is to approve the application, the MAH will be sent updated authorisation documentation, which is comprised of:
- a variation certificate;
 - an updated memorandum document;
 - an updated CTA, if applicable, for biological products only;
 - an updated SPC and product literature, if applicable, and
 - an FPS, if applicable, for pharmaceutical products only.

United Kingdom Public Assessment Report (UKPAR)

252. After a variation has been granted, the public assessment report will be updated to reflect the change. Primarily this will involve recording the variation in the Post Authorisation Assessment document. This will only be applicable to products that were issued after 30 October 2005.

CHAPTER 7

Summary of Product Characteristics (SPCs) and Product Literature

Introduction

253. All MAs include an SPC and product literature, e.g. labels.
254. The SPC and product literature are assessed and approved during the application procedure to obtain a new MA, and any subsequent applications conducted on a product after initial authorisation that affect the SPC and/or product literature, e.g. renewal or variation. However, it should be noted, the labelling of the cartons in which the product literature is packed for distribution to wholesalers and retailers (shipping packs) is **not** assessed.
256. The MAH is responsible for the SPC and product literature of an authorised VMP as set down in the MA. The VMD must approve the SPC and all product literature; any subsequent changes to these documents (including changes to the font of the product literature) may only be made via a variation. However, changes to the labelling that have no effect on the legally required statements and warnings, or their legibility, may be made without the need for a variation, e.g. a change to a barcode would not necessitate a variation.
257. Therefore, the purpose of this chapter is to describe the information required to appear on the SPC and product literature of VMPs placed on the market for sale and supply in the UK, and to outline the procedure for the submission and approval of SPCs and product literature.

Requirements for Product Literature

258. The definition of product literature is as follows:

The **product literature** is the immediate packaging, the outer packaging and the package leaflet (if there is one) -

- The **immediate packaging** is the container or any other form of packaging that is in direct contact with the VMP, e.g. vials, bottles, blister packs, etc. Immediate packaging does not include capsules, which are administered as part of the product.
- The **outer packaging** is the packaging into which the immediate packaging is placed, e.g. cartons, boxes, packets, etc.
- The **package leaflet** is the leaflet that contains information for the user that accompanies the VMP.

259. Applicants should clearly identify the package leaflet as such when submitted for assessment. The package leaflet is different to the data sheet. The VMD does not assess the data sheet, because it is not a requirement under legislation; however

the information in the datasheet must be consistent with the information contained in the approved SPC.

260. The term **mock-ups** includes electronic colour versions, or colour print versions, of the artwork or specimens of the product literature as defined in paragraph 268.

Immediate Packaging

261. The information required on the immediate packaging is outlined in the VMR; if all this information is included on the immediate packaging, there is no need for any outer packaging or a package leaflet. However, if it is not reasonably practicable to include all this information on the immediate packaging, the VMR set out the minimum information that must be included on the immediate packaging. In these cases there will be a need for some outer packaging and, possibly, a package leaflet too.
262. The use of flag or concertina labels on the immediate packaging is acceptable and is one way to provide sufficient space for the required statements and warnings.

Outer Packaging

263. The information required on the outer packaging is also outlined in the VMR. If it is not reasonably practicable to include all this information on the outer packaging, a package leaflet must be supplied with the product.

Package Leaflet

264. If it is not reasonably practicable to include all the required information on the immediate and/or outer packaging, a package leaflet must be supplied with the product. The information required for inclusion in the package leaflet is set out in the VMR.

Ampoules

265. The VMR set out the minimum information required for inclusion on the immediate packaging in the case of ampoules or other small unit dose forms, e.g. tablets in blister packs, where the container cannot have the required information in a size that can be easily read.
266. As above, if all the required information cannot be included on the immediate packaging, some outer packaging will be required. If all the required information cannot be included on the immediate and/or outer packaging, a package leaflet must be supplied with the product.

Small Containers other than Ampoules

267. In the case of small immediate containers, such as vaccine vials or very small volume spot-on products, containing a single dose, other than ampoules or other small unit dose forms, on which it is impossible to give the required information, the container must include at least the batch number and expiry date and as much of the other information stated as possible. All required information must appear on the outer packaging, or outer packaging and package leaflet.

Requirements for Product Literature

268. A list of requirements for product literature for all products intended for sale and supply in the UK is available in the Product Literature Standard on the VMD website http://www.vmd.defra.gov.uk/pharm/guidance_bpg.aspx. Guidance is also included on the use of Quick Response (QR) codes on product literature. Applicants are encouraged to read these documents before submitting product literature (text or mock-ups) to the VMD, because this will expedite the assessment and approval of the application. Non-compliance with the requirements may result in the draft product literature being returned to the applicant for amendment, which will delay the assessment process.
269. For applications for products subject to MRP or DCP, it is particularly important that the applicant considers the labelling requirements at the outset, because some MSs require more than one language to appear on the product labelling; therefore, as a guide, text layouts setting out the required information three times in English should be submitted with the application.

Submission and Approval of Mock-Ups

270. This section provides guidance on the general requirements for the submission and approval of mock-ups for national and EU applications. This should be read in conjunction with the Product Literature Standard.

Format

271. Mock-ups must be submitted electronically. If e-copies are not legible and/or a measurement is not included that indicates what real size packaging is required, applicants will be asked to re-submit the mock-ups.
272. Mock-ups submitted during an application procedure, i.e. not as part of the original application package, should be submitted via email, with the product name(s), application number and EU procedure number (if applicable) clearly marked, to s.response@vmd.defra.gsi.gov.uk.

Incomplete Mock-Ups

273. Your application will be refused at validation if it has inadequate mock-ups (or text). If an application is validated, but later found to have incomplete mock-ups, e.g. missing package leaflet, labels, box or carton, the clock will be stopped at the end of the initial assessment period and the missing data requested. The clock will restart once the missing data have been received.

Mock-ups for Non-Marketed Products

274. Applicants are required to present the product as it is intended to be marketed; if they choose not to market the product then that is their choice. The VMD has to assess whether the application for the product satisfies the criteria set out in the legislation and this includes the assessment of mock-ups.
275. To ease the burden on applicants, the VMD is happy to accept text with applications. If the MAH then decides to market the product they must first obtain VMD's approval of the finalised mock-ups. The assessment of these mock-ups will be dealt with via a variation application, which will attract the normal fee. Similarly, if a MAH only markets some of the authorised pack sizes, then text may be submitted for the non-marketed pack sizes. Again, if the MAH then decides to market one of these pack sizes, it will be necessary to submit a variation application, which will attract the normal fee.

Pack Sizes

276. Mock-ups for all pack sizes, e.g. 50ml, 100ml etc, should be submitted with the application. However, reference should be made to paragraphs 274 and 275 above.

Multi Lingual Packs

277. All labels and package leaflets must be in English. However, they may contain other languages provided that the information given is identical, the requirements of the UK MA are respected, and the legibility of the UK warnings is not compromised.
278. If an MAH wishes to introduce a multi lingual pack for an already authorised product, they must submit the appropriate variation to the VMD in order to have the change approved.

Dedicated Dispensing Container

279. The authorised packaging of a product usually consists of either immediate packaging labelled with all of the required information and warnings, or outer packaging containing a labelled inner container and a package leaflet. Some distributors additionally provide empty, partly-labelled packs, such as envelopes, wallets or cartons for use with specific products. These are intended to be used by veterinary surgeons to supply the dispensed medicines. These product specific (or manufacturer-specific) dispensing containers offer a convenience for the veterinary surgeon. For the company marketing the product, they help to promote the name of the product or the authorisation holder.
280. Where such dedicated dispensing containers are supplied to the veterinary surgeon separately from the authorised pack, they are not subject to the requirements applied to labels and other packaging texts for authorised products. Instead, the usual requirements for labelling of dispensed medicines will apply. However, if the dedicated dispensing containers are enclosed within the authorised packaging, then these are considered to form part of the authorised packaging and subject to scrutiny and approval by the VMD.

281. Veterinary medicines, which fall under the distribution category POM-VPS, may be supplied by Suitably Qualified Persons (SQP). SQPs operating at registered premises must supply the entire contents of the immediate container; they may not supply only part of it, e.g. 200ml of drench from a 500ml pack. However, for certain medicines they may supply a number of immediate containers removed from a larger package as long as package leaflets are provided, for example two vials of vaccine from a pack of 24. In order to clearly identify these veterinary medicines it is intended that the following statements will be introduced into the product literature and SPC:

- Carton/Package Label
- "Individual units of this product may be supplied but each must be accompanied by a package leaflet"
- SPC, section dealing with the packaging
- "Each carton/package contains a sufficient number of package leaflets so that individual units may be supplied by Suitably Qualified Persons"

NATIONAL APPLICATIONS

282. This section outlines the procedure for the submission and approval of product literature for applications dealt with on a national basis only.

283. Wherever possible, mock-ups of the product literature should accompany applications. Mock-ups should reflect the proposed labelling and packaging exactly. The VMD's assessors need to see the mock-ups in order to fully assess the application. This is particularly relevant where sight of the labelling in colour is necessary for the assessment, e.g. where use of colour text could potentially mean that some or all it could be difficult to read or would not adequately draw the eye to the text. However, if the requirement to see mock-ups is not deemed necessary (i.e. for certain variation applications) then text will be accepted. The requirements for individual application types are set out below.

284. It should be noted that if mock-ups are not submitted in a timely fashion, or if the mock-ups are incomplete or incorrect, the application may be issued with a condition that revised mock-ups are submitted to the VMD under cover of a variation application in order that they can be assessed and approved prior to marketing.

New MA Applications

285. The applicant should complete and submit the SPC/Quality Review of Documents (QRD) template, which is available on the VMD website, with the application package; applicants are not required to submit mock-ups at this stage. The absence of the template, or an incomplete or illegible template, may lead to the application being rejected at validation. Once the QRD text has been agreed during the assessment phase, the applicant will be asked to submit mock-ups for approval. The clock will stop pending receipt of mock-ups and will re-start once the correct mock-ups have been received. The mock-ups will be checked and issued with the approval documentation.

Renewal Applications

286. Current product literature should be supplied in order for the application to be validated. For products that are not marketed, text will suffice (see paragraph 275). Please note there should be no proposed changes highlighted on the product literature submitted as part of a renewal application; all changes to product literature must be dealt with by way of a variation application; therefore, the product literature submitted as part of the renewal application should reflect the latest authorised versions.
287. During the assessment process the assessor(s) will identify any changes to the product literature and notify the applicant of these proposed changes in their 'question letter'. The applicant should submit revised versions, incorporating all proposed changes, as part of their company response; if an applicant wishes to query a proposed amendment they should discuss this with the appropriate assessor(s) before submitting their company response. Approved versions will be issued to the applicant with the rest of the authorisation documentation once the application has been approved.

Variation Applications

288. If the variation affects the product literature then the current packaging should be supplied, accompanied by draft versions of the relevant product literature showing the proposed changes. The term "draft" refers to the same mock-up, but in black and white, i.e. the artwork, size, format and layout are the same; the only difference is the lack of colour. Failure to supply these items, if required, will result in an invalid application.
289. The criterion for granting or refusing an application for a variation is simply whether the proposals will adversely affect the safety, quality and efficacy of the authorised product. It is a matter of judgement, depending upon the nature of the variation, e.g. any change that would alter the labels' content or size, as to whether the VMD needs to see mock-ups during the assessment. If mock-ups are required then the assessors will request these during the assessment process. Where changes to the mock-ups are required, the assessors will inform the applicant of this.
290. Once the application has ended the approved versions will be issued to the applicant along with the rest of the authorisation documentation.

EU APPLICATIONS

291. This section outlines the procedure for the submission and approval of product literature for applications dealt with on an EU basis only.
292. Applicants should submit proposed label(s) and package leaflet text in the QRD template as part of the application package; this will be reviewed and agreed by all CMSs during the application procedure. Upon completion of the application procedure, the applicant will be required to submit mock-ups (if applicable) reflecting the agreed text (including any national requirements, e.g. legal category) to each MS, who will progress the application on a national basis.
293. If amendments are required, revised mock-ups will be requested. This process may happen several times until the assessor is happy with the mock-ups provided.
294. If the UK and Ireland are involved in an application procedure, it will be assumed that the applicant would like to achieve joint-labelling unless they advise the VMD otherwise. Joint labelling is when the UK and Ireland approve one set of labels for use in both the UK and Ireland. Further information about the joint-labelling procedure is available in a clarification paper available on the VMD website.
295. It should be noted that if mock-ups are not submitted in a timely fashion, or if the mock-ups are incomplete or incorrect, the application may be issued with a condition that revised mock-ups are submitted to the VMD under cover of a variation application in order that they can be assessed and approved prior to marketing.

GENERAL INFORMATION

296. Before issuing approved mock-ups the VMD will amend the header to include the date that the application was issued for new applications, or the date the MA was revised for variation and renewal applications, plus the application number, e.g. Issued/Revised April 2008 - AN 01234/2008. This will show on each page and will help maintain version control of the document.

Introducing Changes to the market place

297. MAHs have **six months** from the grant of an application to introduce revised product literature to the market place; if an alternative timescale is agreed this will be shown on the authorisation certificate issued at the end of an application procedure. Shorter timeframes will usually apply if the change concerned relates to a safety issue, e.g. the introduction of a longer withdrawal period. Requests for longer timeframes should be made at the time of application; if MAHs wish to request an extension to the timeframe following grant of the application, they should do so BEFORE the deadline is reached and via email to a member of the Licensing Administration Branch.

Requirements for Summary of Product Characteristics (SPC)

298. The requirements for SPCs are detailed in the VMR. MAH should also refer to the guidelines set out in *Volume 6c of the Notice to Applicants*, which is available on the EMA website, when producing their SPC.

- *Guideline on Summary of Product Characteristics SPC - Pharmaceuticals for VMP (volume 6C: Regulatory Guidelines)*
- *Guideline on Summary of Product Characteristics SPC - Immunologicals for VMP (volume 6C: Regulatory Guidelines).*

Sections 1, 9 and 11 of the SPC

299. The VMD is aware that it is not totally clear what is required in Sections 1, 9 and 11 of the SPC. Therefore, we are providing the following information to ensure a consistent approach.
300. The following will apply to applications for new MAs authorised on a national basis only, and any subsequent renewal or variation applications conducted on these MAs where SPC changes are required.

Section 1 (Product Name)

The product name should not be written in block capitals.

Pharmaceutical products: Name + strength + pharmaceutical form + target species, if necessary.

Immunological products: Name + vaccine strain (if necessary/relevant) + target species (if necessary/relevant).

Section 9 (Date of first authorisation/date of the renewal of the authorisation)

Date of first authorisation: This applies to both pharmaceutical and immunological products.

Section 11 (Further information)

This is a national requirement only.

The text 'Section 11' will not be included in the SPC. The VMD (not the applicant) will add 'Section 11', plus the relevant information, in exceptional circumstances only.

This applies to both pharmaceutical and immunological products.

The following are examples of what the VMD would consider appropriate:

- a) Reference to specific requirements relevant to the PET Travel Scheme;
- b) Restrictions to the supply of the product subject to national or EU control measures.

Submission and Approval of SPCs

NATIONAL APPLICATIONS

301. The purpose of this section is to outline the procedure for the submission and approval of SPCs for applications dealt with on a national basis only.
302. Applicants are required to submit a draft SPC with an application whether it is for a new, renewal or variation procedure (where the proposed change affects the SPC). For new applications, the applicant should complete and submit the SPC/QRD template, which is available on the VMD website, with the application package. For variation and renewal applications only the SPC part of the template should be submitted. SPCs must be submitted in Word format. The absence of this template, an incomplete or illegible template, or it not being submitted in Word format may lead to the application being rejected at validation.
303. The SPC will be agreed during the assessment phase of an application procedure. Once the application has been approved the VMD will update the electronic Summary of Product Characteristics (eSPC) on behalf of applicants. The approved version will be issued to the applicant along with the rest of the authorisation documentation. The website will then be updated to show the latest authorised version.

EU APPLICATIONS

304. The purpose of this section is to outline the procedure for the submission and approval of SPCs for applications dealt with on an EU basis only.
305. Applicants should submit SPC in accordance with the guidance provided in the *Best Practice Guides* available on the HMA website.
306. The applicant should send a copy of the finalised SPC to the RMS/CMSs at the end of an EU procedure. There should be no changes to the SPC once the EU procedure is ended and MSs cannot request amendments to the SPC after this point. However, if the applicant has not updated the SPC in accordance with what was agreed during the procedure, we will go back to them (or to the RMS if we are a CMS) and ask them to update it properly.

GENERAL INFORMATION

307. Before issuing an approved eSPC the VMD will amend the header to include the date that the application was issued for new applications, or the date the MA was revised for variation and renewal applications, plus the application number, e.g. Issued/Revised April 2008 - AN 01234/2008. This will show on each page and will help maintain version control of the document.
308. For national new applications, we will ensure section 9 (Date of First Authorisation) of the SPC accurately reflects the date the MA was granted.
309. For all national applications, we will amend section 10 (Date of Last Revision) of the SPC to reflect the header.

310. For EU applications, we will ensure that sections 7, 8, 9 and 10 of the SPC are up-to-date and accurate before issue. These are the so-called national sections of the SPC, i.e. the information in these sections can be different across MSs.
311. For all applications (national and EU), the agreed SPC will then be retained as the latest version and published on the VMD website in accordance with the VMR.

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CHAPTER 8

Submission of Applications

General Information

312. MAHs are strongly advised to contact the VMD prior to the submission of an application for a new MA. In most cases it is advisable for the proposed MAH to come in for a meeting with the relevant VMD personnel in order to discuss the content and structure of the application package; however, it is the applicant's responsibility to ensure they have reviewed all relevant information available to them prior to requesting and/or attending a meeting with VMD staff.
313. MAHs may submit their application packages, which includes the application form and supporting data, to the VMD either electronically (an e-submission), or in hard-copy. However, we strongly encourage applicants to submit their application packages electronically. It should also be noted that the SPC must be submitted electronically and in Word format regardless of how the rest of the application package is submitted; failure to do so will result in the application being deferred at validation pending receipt of a correct version.
314. If submitted electronically, the media on which to provide the e-submission is described in the European guideline prepared by the Telematics Implementation Group for e-Submission-Vet (TIGes-Vet Sub Group), which is available on the EMA and VMD websites. An e-submission may also be sent via e-mail (using Eudralink or not; it is the applicant's choice) to: s.response@vmd.defra.gsi.gov.uk. Note there is a 80MB limit on the Eudralink system and a 25MB limit on normal emails, i.e. not sent via Eudralink.
315. If submitted in hard-copy the MAH should send the application package to the following address:
- Information Services
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey
KT15 3LS
316. Application forms are available on the VMD website.
317. Queries regarding the submission of applications should be directed to the Information Management team via email to: s.response@vmd.defra.gsi.gov.uk.

Applications for New MA

Full and Abridged

318. If submitting electronically, the structure of the e-submission should be in line with the requirements of the (TIGes-Vet) guideline.

319. If submitting in hard-copy, please provide the following:
- For pharmaceutical products we require one copy of the application form and data package.
 - For immunological products we require one copy of the application form and data package including the expert report.
320. The same application form should be used for an application for a new MA submitted to:
- (a) the EMA under the centralised procedure, or
 - (b) a MS under a national procedure, or under a mutual recognition or decentralised procedure.

Exceptional MA

321. If submitting electronically, the structure of an e-submission should be in line with the requirements of the (TIGes-Vet) guideline; however, certain folders may be deleted as necessary depending on the data submitted with the application.
322. If submitting in hard-copy, please provide the following:
- For pharmaceutical products we require one copy of the application form and data package.
 - For immunological products we require one copy of the application form and data package including the expert report.
323. The application form is a VMD-created document for use under this national-only scheme and is available on the VMD's website.

MAPI

324. If submitting electronically, the structure of an e-submission should be in line with the requirements of the TIGes-Vet guideline; however, certain folders may be deleted as necessary depending on the data submitted with the application.
325. If submitting in hard-copy, please provide one copy of the application form and data package.
326. The application form is a VMD-created document for use under this national-only scheme.

Renewal Applications

327. If submitting electronically, the structure of an e-submission should be in line with the requirements of the TIGes-Vet guideline.
328. If submitting in hard-copy, please provide one copy of the application form and data package for both National & EU renewals.

329. The application form for renewal of a nationally authorised MA, which is a VMD-created form for use under this national-only scheme, is different to the form used for renewal of a mutually recognised MA.

Variation Applications

330. If submitting electronically, the structure of an e-submission should be in line with the requirements of the TIGes-Vet guideline.
331. If submitting in hard-copy, please provide one copy of the application form and supporting data for Type IA, Type IB (single or grouped), and Type II variations (single, grouped or work-sharing).
332. For variation Extension applications (single or grouped), please provide one copy of the application form and supporting data for pharmaceutical and immunological products. If the Extension application is part of a grouped variation, the EU variation application form should be included as an appendix to the MA application form.
333. The same application form should be used for an application to vary an MA under a national variation, or mutual recognition variation procedure. This form should also be used when submitting a national unforeseen variation.

Fees

334. The fee should not accompany the application and nor should it be paid in advance of the submission of the application. Fees are payable on receipt of an invoice.
335. Details on the relevant fees can be found in the VMR, which are available on the VMD website www.vmd.defra.gov.uk. The VMD has also produced a calculator to enable applicants to determine what the fee for their application will be. This is also available on the VMD website at: <http://www.vmd.defra.gov.uk/pharm/fees.aspx>

Further Information

336. Further information is available from the Veterinary Medicines Directorate, Woodham Lane, New Haw, Addlestone, Surrey, KT15 3LS - Tel: +44 (0)1932 336911; Fax: +44 (0)1932 336618 or E-mail: VMGNotes@vmd.defra.gsi.gov.uk. Veterinary Medicines Guidance Notes and other information, including details of VMD contacts, are available on the VMD website (www.vmd.defra.gov.uk).

List of Abbreviations

AE	Adverse Event
CMS	Concerned Member State
CTA	Controlled Test Appendix
CMDv	Co-ordination Group for Mutual Recognition & Decentralised procedures-Vet
CVMP	Committee for Medicinal Products for Veterinary Use
DCP	Decentralised Procedure
DDPS	Detailed Description of the Pharmacovigilance System
defra	Department for Environment, Food & Rural Affairs
EC	European Commission
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
ExMA	Exceptional MA
FPS	Finish Product Specification
HMA	Heads of Medicines Agency
IVMP	Immunological Veterinary Medicinal Product
LMA	Limited Marketing Authorisations
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
ManA	Manufacturer's Authorisation
MAPI	Marketing Authorisation Parallel Import
MRL	Maximum Residue Limit
MRP	Mutual Recognition Procedure
MSDS	Material Safety Data Sheets
MS	Member State
MUMS	Minor Use Minor Species
PMA	Provisional Marketing Authorisation
POM-V	Prescription Only Medicine - Veterinarian
POM-VPS	Prescription Only Medicine - Veterinarian, Pharmacist, Suitably Qualified Person
PSUR	Periodic Safety Update Report
QP	Qualified Person
QRD	Quality Review of Documents
RMS	Reference Member State
SLE	Suspected Lack of Efficacy
SPC	Summary of Product Characteristics
SQP	Suitably Qualified Person
UKPAR	United Kingdom Public Assessment Report
VMD	Veterinary Medicines Directorate
VMGN	Veterinary Medicines Guidance Note
VMP	Veterinary Medicinal Product
VMR	Veterinary Medicines Regulations
VPC	Veterinary Products Committee
WDA	Wholesale Dealers Authorisation

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VETERINARY MEDICINES GUIDANCE NOTE

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Search for VMD on www.gov.uk