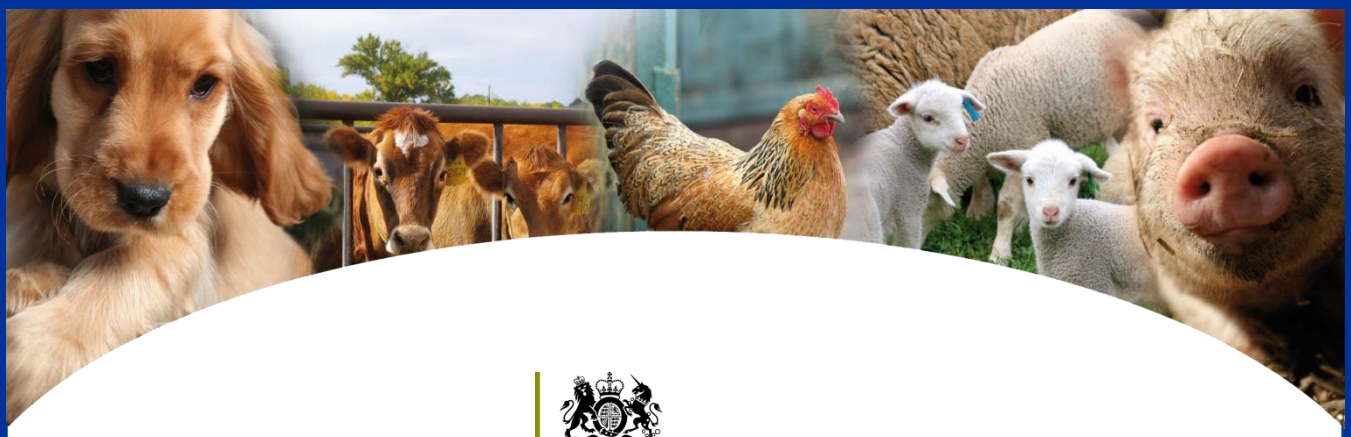

Veterinary Medicines Directorate

Document Withdrawn as out of date. Please refer to guidance at [Veterinary medicines guidance - GOV.UK]

GUIDANCE ON THE HOMEOPATHIC REGISTRATION SCHEME

Last updated September 2011

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 homeopathic remedies, who wish to seek registration of those remedies with the Veterinary Medicines Directorate (VMD).

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 VMR allow homeopathic remedies to be placed on the market, provided one of the following criteria is met:

- the remedy, as manufactured by a specified manufacturer, may be registered with VMD through the registration scheme;
- the remedy may have 'grandfather rights' and have been included in the list of such remedies as manufactured by a specified manufacturer;
- the remedy may be prepared extemporaneously and supplied directly to the end user by a pharmacist in a registered pharmacy in accordance with a homeopathic manufacturing procedure described in an official European Pharmacopoeia (Ph.Eur.);
- the remedy may be prescribed by a veterinary surgeon and either already registered or authorised for human use or have been prepared extemporaneously in accordance with the provisions of the cascade.

At present remedies classified as sarcodes (homeopathic remedies prepared from healthy animal tissues and secretions) or nosodes (homoeopathic remedies prepared from microbe cultures, from viruses, fungi, pathological secretions and excretions) are not considered to fall within any of the above categories.

FURTHER INFORMATION

- 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

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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.

3. This VMGN explains the procedures for the registration of homeopathic remedies, together with other ways in which homeopathic remedies may be placed on the market in the UK. The registration scheme provides a procedure for homeopathic remedies to be placed on the market, with no stated therapeutic indications and where there is sufficient dilution to guarantee the safety of the remedy.

4. Unless otherwise specified, all documents available on the Veterinary Medicines Directorate's (VMD's) website will be found in the thematic area, 'Pharmaceutical Industry'

CHAPTER 1

What is the Homeopathic Registration Scheme?

5. A veterinary homeopathic remedy (VHR) is a veterinary medicinal product (VMP) prepared from homeopathic stocks in accordance with a homeopathic manufacturing procedure. As long as it meets the criteria set out in the VMR, a VHR must be the subject of a valid homeopathic registration before it can be placed onto the UK market for sale and supply.

6. An application for a VHR should normally be made by the proposed Registration holder who must be established within the European Community ('the Community'). For companies this means they must be formed in accordance with the law of a Member State (MS) and have their registered office, central administration, or principle place of business within the Community. The Community includes all countries in the European Economic Area (EEA) including Norway, Iceland and Liechtenstein.

7. Manufacturers of VHR require authorisation in order to manufacture the remedies. For further information please refer to VMGN 15 Guidance for Manufacturers, which is published on the VMD's website.
http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

8. Not all remedies for which applications are submitted are granted Registrations. Some applications for VHR 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 Vh Symbol

9. A registered product will have a registration number preceded by the symbol Vh on its product literature, e.g. labels; this offers users a clear guarantee that the VHR has been assessed and approved in accordance with the instructions on the product literature.

Distribution Categories

10. A registered product will also have a distribution category, which relates to the retail supply of a product, e.g. a product classified as POM-V (Prescription Only Medicine – Veterinarian) may only be supplied by a veterinary surgeon or a pharmacist and must be supplied in accordance with a prescription from a veterinary surgeon. However, it is normally expected that most remedies will be distributed through the AVM–GSL (Authorised Veterinary Medicine – General Sales List) category which allows products to be sold "off the shelf". 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 a Registered VHR

11. A registered VHR is valid for five years following grant of the initial Registration. After this time the Registration must be renewed in order for it to continue to be registered. If a registered VHR is not renewed by the renewal date it will cease to be valid.

12. Once renewed the Registration 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 Registration is revoked or expired. Further information about renewals is available in chapter 5.

13. Where a registered VHR is not marketed in the UK for three consecutive years, the Registration will cease to be valid unless, exceptionally, an exemption from this provision is granted on justified human or animal health grounds. This provision is known as the 'sunset clause'; the VMD will contact Registration holders about products subject to the sunset clause in order to discuss a way forward and before taking any action.

14. During the validity of the VHR, evidence may become available which throws doubt on the safety or quality of the product, or which alters the benefit:risk assessment. In such circumstances the VMD may revoke, suspend or compulsorily vary the Registration. 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 a Registration holder has changed any of the approved specifications of a registered product without the prior approval of the VMD, the Registration 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 Registration.

Manufacturing Authorisation (ManA)

15. Registered VHR must be manufactured by a person holding a ManA that covers the manufacture of this type of product. The provisions in the VMR that relate to possession, manufacture, supply, administration and pharmacovigilance apply in exactly the same way as they do to any other VMP.

Placing a VHR on the Market

16. There are several ways in which homeopathic remedies may be placed on the market in the UK:

    (a) the remedy, as manufactured by a specified manufacturer, may be registered with the VMD through the registration scheme;
    (b) the remedy may have 'grandfather rights' and have been included in the list of such remedies as manufactured by a specified manufacturer (see paragraph 23);
    (c) the remedy may be prepared extemporaneously and supplied directly to the end user by a pharmacist in a registered pharmacy, in accordance with a homeopathic manufacturing procedure described in an official European Pharmacopoeia (Ph.Eur.);
    (d). the remedy may be prescribed by a veterinary surgeon and either already registered or authorised for human use, or have been prepared extemporaneously in accordance with the provisions of the cascade.

17. At present remedies classified as sarcodes or nosodes are not considered to fall within any of the above categories.

Remedies that are Eligible for Registration

18. A single Registration may cover multiple dosage forms and routes of administration and different degrees of dilution providing they are all derived from the same homeopathic stock or stocks. To be eligible for registration a VHR must be:

    - prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described in an official European pharmacopoeia;
    - administered by a route described in such a pharmacopoeia, such as an oral or topical form;
    - sufficiently diluted to guarantee safety, that is, may not contain more than 1 part in 10,000 of the mother tincture.

19. Multiple dosage forms, multiple routes of administration and different degrees of dilutions may be covered by a single registration provided they are all derived from the same homeopathic stock or stocks.

VHR not subject to the Homeopathic Registration Scheme

20. It is not necessary to register all VHRs under the Scheme. Remedies made in other ways, as described in paragraph 16, are outside the scope of the scheme and are covered separately.

21. However, there are additional categories of remedy which are also treated differently:

    - remedies making specific therapeutic claims, including immunological claims
    - remedies not considered sufficiently dilute to guarantee safety
    - the route of administration is not as described in the Ph.Eur. or an official pharmacopoeia of a MS

22. These are considered to fall within the normal definition of a VMP and, therefore, require an MA before they can be placed on the UK market for sale and supply, for further information please refer to VMGN 2 Marketing Authorisations for Veterinary Medicinal Products, which is published on the VMD's website.
    http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

Grandfather Rights

23. Any remedy that was placed on the UK market before 1 January 1994 may continue to be manufactured and marketed without being registered.

24. These remedies have so called "Grandfather Rights" provided they have been entered onto the list held by the VMD. It is the responsibility of the manufacturer to have advised the VMD that the remedy is eligible for these rights and have made a declaration to that effect, so that the remedy has been placed on the list. The list of remedies eligible for "Grandfather Rights" is available on the VMD's website.
    http://www.vmd.defra.gov.uk/pharm/homeopathic.aspx

CHAPTER 2

Types of Registration

25. There are three different routes to obtaining a Registration under the Homeopathic Registration Scheme; these routes determine the procedures, processes and timelines used in progressing an application for a new VHR in accordance with legislation. Once granted, the Registration will be classified as nationally registered, or mutually recognised.

Registration Route	Registration Type
A national procedure	the product will be classed as "nationally registered".
The Mutual Recognition procedure	the product will be classed as "mutually recognised".
The Decentralised procedure	the product will also be classed as "mutually recognised".

Nationally registered VHR

26. A product that has been assessed and approved on a national basis only, i.e. there has been no interaction with other European Union (EU) MS.

Mutually recognised VHR

27. A mutually recognised product is one that has been assessed and approved on a European level involving at least two EU MS, i.e. evaluated via the mutual recognition or decentralised procedure.

28. The mutual recognition procedure (MRP) is a European registration route resulting in a mutually recognised product.

29. Mutual recognition must be used when a product is already registered in at least one EU MS on a national basis and the Marketing Authorisation Holder (MAH) wishes to obtain a Registration for the same product in at least one other EU MS

30. The MS that has already registered the product is known as the Reference Member State (RMS). The RMS submits their evaluation of the product to the other MS(s); known as a Concerned Member State(s) (CMS). The CMS is asked to mutually recognise the Registration of the RMS.

31. If the application is successful, the CMS will then issue a Registration for that product permitting the marketing of that product in their country.

32. Please note if the UK acts as RMS this means the product was initially registered in the UK on a national basis first; therefore, once the mutual recognition procedure has been successfully completed, the registration type of the UK product will change from 'National' to 'Mutually Recognised'.

33. The decentralised procedure (DCP) is a European registration route resulting in a mutually recognised product.

34. The difference between MRP and DCP is that a product must already be registered 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 registered in any EU MS and a company wishes to register it in several or all EU MS.

35. One of the proposed MS will be asked by the Registration holder 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 issued. The CMS either agree with the RMS's evaluation or they ask further questions/raise objections.

36. If all the issues are resolved and the application is successful, each MS will then issue a Registration for that product permitting it to be marketed in their country.

CHAPTER 3

Product Literature, e.g. labels

37. All registered VHR must be labelled in accordance with the requirements set out in the VMR.

38. The product literature is assessed and approved during the application procedure to obtain a new Registration, and any subsequent applications conducted on a VHR after initial registration that affects the product literature, e.g. renewal or variation.

39. The Registration holder is responsible for the product literature of a Registered VHR as set down in the Registration. The VMD must approve the product literature; any subsequent changes to these documents (including changes to the font or layout of the product literature) may only be made via a variation application, for further information please refer to VMGN 2 Marketing Authorisations for Veterinary Medicinal Products, which is published on the VMD's website.
http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

40. 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.

Requirements for Product Literature

41. 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 product, 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 VHR.

42. 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 45.

43. A list of requirements for product literature for all products intended for sale and supply in the UK is available on the VMD's website, www.vmd.defra.gov.uk
Applicants are encouraged to read this document before submitting product literature (text or mock-ups) to the VMD, because this may 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.

Requirements for National Applications

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

45. 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.

46. 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.

Applications for New Registrations

47. At the time of application, where possible, mock-ups accompanied by text should be submitted with an application for a new Registration. Where this is not possible, text should be submitted before the application can be validated. However, mock-ups must be submitted before the assessors can sign off an application. The assessors will deal with the submission of mock-ups during the assessment period and will inform the applicant of any required changes.

48. Amended versions will be sent to the applicant at the end of the assessment period, i.e. once all assessors have signed off an application. The assessment 'clock' will stop pending receipt of revised mock-ups and will re-start once the correct mock-ups have been received. Revised mock-ups will be checked and issued with the registration documentation.

Renewal Applications

49. 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 56). 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.

50. 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. In the case of renewals, where a timescale for the introduction of any required changes has been agreed, this will be indicated on these documents.

Variation Applications

51. 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 printed 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.

52. The criterion for granting or refusing an application for a variation is simply whether the proposals will adversely affect the safety or quality of the registered 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.

53. Where changes to the mock-ups are required, the assessors will inform the applicant of this and also a date by which the revised product literature should be introduced to the market place. Unless requested, revised versions of the mock-ups do not need to be submitted to the VMD following the approval and issue of the variation application.

54. When the VMD approves labels and package leaflets these will be signed, dated and returned to you. In the case of variations, where a timescale for the introduction of any required changes has been agreed, this will be indicated on these documents.

Requirements for EU Applications

55. This section outlines the procedure for the submission and approval of product literature for applications dealt with on an EU basis only

56. Applicants should submit proposed label(s) and package leaflet text in the Quality Review of Document (QRD) template as part of the application package; this will be reviewed and agreed by all CMS 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. The mock-ups should be accompanied by a completed checklist, which is available on the VMD website.

57. If amendments are required, revised mock-ups will be requested. This process may happen several times until the assessor(s) is happy with the mock-ups provided. It should be noted that mock-ups may be approved with minor annotated amendments, e.g. typographical errors; mock-ups do not have to be 'clean', although this is the preference. It is a matter of judgement, depending upon the nature of the proposed changes, as to whether the VMD needs to see revised mock-ups before signing off the application.

58. 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 http://www.vmd.defra.gov.uk/pharm/guidance_clarification.aspx .

59. 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.

CHAPTER 4
The Application Process

Submission

60. Proposed Registration holders are strongly advised to contact the VMD prior to the submission of an application for a new Registration. In most cases it is advisable for the proposed registration holder 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.

61. Applicants 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.

62. If submitted electronically, the media on which to provide the e-submission is described in the *European guideline prepared by the TIGes-Vet Sub Group*, which is available on the European Medicines Agency (EMA) website, http://esubmission.ema.europa.eu/tiges/vetesub.htm. An e-submission may also be sent via email (via Eudralink or not; it is the applicant's choice) to: s.response@vmd.defra.gsi.gov.uk.

63. If submitted in hard-copy the applicant should send three copies of the application package to the following address:

    Information Management Section
    Veterinary Medicines Directorate
    Woodham Lane
    New Haw
    Addlestone
    Surrey
    KT15 3LS

64. The application forms are available on the VMD website.

65. Queries regarding the submission of applications should be directed to the Information Management team via email to: s.response@vmd.defra.gsi.gov.uk.

Timescales

66. The timescales for dealing with an application for a new Registration on a national basis only are set out below. The procedures and timescales for dealing with an application for a new Registration via MRP or DCP are the same as those used for a new MA, which are outlined in the *Best Practice Guides* available on the Heads of Medicines Agency (HMA) website, http://www.hma.eu/veterinary.html

67. Applications for new Registrations, dealt with on a national basis only, are subject to a 10-day validation period. If the application is incomplete the application will either fail validation and the applicant will be asked to resubmit the application, or the validation clock will stop and the applicant will be asked to provide the outstanding data. Once received the validation clock will restart at 0. In both cases, the applicant will be informed accordingly.

68. Once the application is deemed valid, the application will be processed on a 50-day timetable and the clock will start running in the assessment phase where the assessor(s) has up to 30 days to either approve or refuse the application, or ask further questions. Whatever the outcome, the applicant will be informed accordingly.

69. If further questions are asked, the clock will stop pending receipt of the response. The applicant will be asked to provide a response within a given deadline (usually three months, or other timescale as agreed by the VMD); if a response is not received within the given deadline, the application will be considered withdrawn.

70. Upon receipt of a complete response, the clock restarts and the assessor(s) has a further 20 days to assess the response and either approve or refuse the application. If approved, formal registration documentation will be sent to the applicant within 10 days of assessor sign-off.

71. There is provision for stopping the clock during an application procedure if further information/clarification is required.

Data Requirements and Validation

72. The data and documents required in support of an application for a new Registration dealt with on a national basis are provided in the application forms and the annex to this VMGN. All data should be submitted in two separate volumes as outlined below:

Volume 1:

- ManA number
- A copy of any registrations or authorisations by other EC Member states
- A copy of any registrations granted for the remedy under the equivalent human registration scheme
- Proposed product literature, e.g. labelling

Volume 2:

- Production and control of homeopathic stocks
- Production and control of dosage form
- Stability of the dosage form
- Data to support withdrawal periods

73. Applicants may make cross-references to relevant studies in the data dossier for an already registered VHR, which is held by the VMD and to which the applicant has a right of access.

74. The data and documents required in support of an application for a new Registration dealt with via MRP or DCP are detailed in *Volume 6 of the Notice to Applicants*, http://ec.europa.eu/health/documents/eudralex/vol-6/index_en.htm

75. All applications for Registrations are subject to validation; guidance on how to submit a valid application is provided on the VMD website.

76. 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.

Assessment and Outcome

77. 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.

78. For applications dealt with via MRP or DCP – if one or more of the CMS considers the benefit:risk assessment to be unsatisfactory, the application may be referred to CMDv (Co-ordination group for Mutual recognition and Decentralised procedures – veterinary) for further discussion. Further information about the referral process is available in a *Best Practice Guide available on the HMA website*. In the decentralised procedure, if the RMS after assessment reaches a negative benefit:risk conclusion, then the procedure ends. Appeals may only be made under national procedures.

79. 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

80. If the outcome is to approve the application, the applicant will be sent authorisation documentation, as follows:

<u>Following completion of an MRP Application – UK as RMS</u>

- A letter
- An updated memorandum document
- Updated and approved product literature, and
- An updated Finished Product Specification (FPS), if applicable, for pharmaceutical products only

<u>Following completion of all other applications</u>

- A certificate
- A memorandum document
- Approved product literature, and
- An FPS, for pharmaceutical products only

Fees

81. The fee should not accompany the application and nor should it be paid in advance of the submission of the application.

82. Details on the relevant fees can be found in the VMR, which are available on the VMD website.

Post-Authorisation Steps

83. Following it being granted, the Registration may be subject to a number of post-registration requirements including renewal, variation procedures that facilitate any proposed changes to the particulars and the requirement to report adverse events (AE). Further information about post-registration steps is available in Chapter 5.

CHAPTER 5
Post-Registration Steps

Pharmacovigilance

84. Pharmacovigilance requirements for homeopathic remedies, including products eligible for "grandfather rights", are the same as for products with MAs. For further information please refer to 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

Variations

85. Any changes to the terms or conditions of a Registration must be made by means of a variation, unless otherwise agreed by the VMD. For example, if you wish to extend the shelf life of the product this would constitute a variation. However, an addition of a further stock (regardless of whether or not it has been previously registered or assessed) is not considered to be a variation, and an application for a new registration should be submitted.

86. The procedure for varying a Registration is the same as it is for varying an MA. For further information please refer to VMGN 2 Marketing Authorisations for Veterinary Medicinal Products, which is published on the VMD's website:
http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

Duration and Renewal of Registrations

87. A Registration is valid for five years following grant of the initial Registration. After this time the Registration must be renewed in order for it to continue to be authorised. If a Registration is not renewed by the renewal date it will cease to be valid.

88. The VMD will endeavour to send a reminder letter to the Registration holder, but these are sent as a courtesy and it remains the responsibility of the Registration holder to apply for renewal at the appropriate time.

Changes to a Registration

89. Changes to a Registration that affect the product literature cannot be made during the renewal process; in order to ensure a Registration is as up-to-date as possible, any changes to the Registration 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 Registration ceases to be valid.

90. 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 Registration accordingly, which may be charged for and processed as per normal procedures.

91. Please note that a renewal application will not be accepted while the Registration is subject to ongoing variation procedures, which affect the product literature, and variation applications that affect the product literature will not be accepted while the Registration is subject to a current renewal procedure.

The Application Process

Submission and Validation

92. Applications may be submitted either electronically (an e submission), or in hard-copy as per the guidance provided in chapter 4 ('Submission').

93. For mutually recognised Registrations, a renewal application should be submitted to the RMS and CMSs at least six months prior to the date of renewal.

94. The applicant must complete all parts of the application form, which is available on the VMD website.

95. 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*.

96. For nationally registered VHR, a renewal application should be submitted to the VMD at least nine months prior to the date of renewal.

97. The applicant must complete all parts of the application form, which is available on the VMD website.

98. A list of the data and documents required in support of an application for renewal of a nationally registered VHR is available on the VMD website.

99. All renewal applications are subject to validation; guidance on how to submit a valid application is provided on the VMD website.

100. Further information about the criteria for submitting product literature is provided in Chapter 3.

101. The onus is on the Registration holder to identify and submit all the necessary supporting data in their application package. If the application is incomplete it is likely to fail validation.

102. Once the application is deemed valid it will proceed into the assessment phase.

Assessment and Outcome

103. 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/51.html . The procedures and timescales used for the assessment of applications dealt with on a national basis are the same as those used for renewing an MA.

104. For applications dealt with via the MRP – if one or more Member states considers 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*.

105. For applications dealt with on a national basis - If the proposed outcome is to refuse the application, the Registration holder will be notified of this and given an opportunity to discuss this with the VMD before the decision is implemented.

106. If the outcome is to approve the application, the Registration holder will be sent registration documentation, which is comprised of:

- A renewal certificate
- An updated memorandum document
- Updated and approved product literature, if applicable, and
- An FPS, if applicable, for pharmaceutical products only

107. Once renewed the Registration 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 Registration is revoked or expired.

108. For products which have been mutually recognised or national products which may subsequently go through the mutual recognition process, the Registration holder may be required to submit further renewals even if the Registration has an unlimited life in the UK. This is because the registrations issued in other MS 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.

Fees

109. The fee should not accompany the application and nor should it be paid in advance of the submission of the application.

110. Details on the relevant fees can be found in the VMR, which are available on the VMD website

Further Information

111. 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).

ANNEX A

ACCOMPANYING DATA FOR NATIONAL APPLICATIONS

Data Required to Accompany the Application Form

Remedy Details:

- Scientific name (or other name used in a pharmacopoeia) of the homeopathic stock(s).
- Pharmaceutical form.
- Route of administration.
- Degree of dilution to be registered.

Production and Control of Homeopathic Stocks

- A dossier describing how the homeopathic stock(s) is/are obtained and controlled.
- Bibliographic justification of the homeopathic nature of the stock(s).

The homeopathic stock should be named, with reference to an appropriate pharmacopoeial monograph. It must be prepared from products, substances or compositions called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the Ph.Eur. or, if it is not described there, in a pharmacopoeia published by the British Pharmacopoeial Commission.

Please provide information on the source material (e.g. name of supplier, batch data), details concerning the preparation of the homeopathic stock, and batch data. In some cases additional information may be requested before the application is approved.

The homeopathic nature of the stocks used to prepare remedies should be justified by reference to a recognised homeopathic bibliography.

Where remedies contain substances which are of animal origin, it is necessary to include a description of all the methods taken to ensure the absence of pathogens from within that substance. Reference should also be made to the European Commission *'Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3)*', (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003700.pdf) and details should be provided of the relevant controls applied.

If any of the stocks you are using are, themselves, registered homeopathic remedies, you must provide the full registration numbers of these remedies.

Raw materials and vehicles used should be of an appropriate pharmacopoeial quality unless adequately justified.

The quantity of raw materials and vehicles used for each batch should be specified. If batch sizes vary, then a representative batch size should be stated.

The nature of containers used for the maceration process should be described, together with the times and conditions used.

Control of Starting Materials

Raw Materials
Raw materials used should comply with the section on raw materials set out in individual monographs of a homeopathic pharmacopoeia.

In some instances it may be necessary to include additional controls for monographed raw materials, for example:

Plant Material

* Microscopic examination.
* Limit tests for pesticides - details of all pesticides used should be given
* Description of the part of the plant used
* Details of the geographical source of the plants and details of the cultivation methods and collection of plants/plant parts.
* Documentation should be provided to demonstrate that full testing for compliance with all specifications of source materials has been carried out.

Minerals of Natural Origin

* Bioburden controls and proof of the absence of pathogens.

Zoological Material

* Details of animal husbandry should be given.
* Details of the collection method of materials should be given.
* Documentary proof to demonstrate the absence of pathogens, fungal, bacterial and, wherever possible, viral contamination should be provided.

It is recognised that where companies purchase materials from elsewhere, some of the necessary documentation may not be forthcoming. In such cases companies can arrange for information to be sent, on a commercially restricted basis, directly to the VMD by the suppliers. Alternatively, if this is not possible, then applicants must demonstrate the quality of the starting materials that they use by providing details of the inspection and tests that they have carried out to verify that the materials meet the given specifications.

Botanical Nomenclature

The botanical identity of materials must be clearly defined. In order to avoid confusion and to facilitate easy passage of applications for remedies containing botanical materials, this reference should, wherever possible, be to the currently accepted names, synonyms and botanical authorities quoted in the *'Index Kewensis'*.

Additional Information

Applicants should provide data to demonstrate compliance with the agreed monograph (batch data or certificates of analysis for three batches). Where additional controls are necessary, evidence should be provided to show that these controls have been met.

Supporting data for plant material should include details of the source of the material, cultivation and time of harvesting. Details of any drying procedure used, and any treatment to reduce levels of microbial contamination should be stated. It is preferable for plant material to be grown organically.

Supporting data for zoological material should include information on the collection, treatment and storage of the source material.

Vehicles

Vehicles used for the preparation of homeopathic stocks should be of an appropriate pharmacopoeial specification unless justified.

Control of Stocks

A specification should be provided for each stock.

Applicants should provide satisfactory evidence in the form of batch data or certificates of analysis to demonstrate that the stock meets the agreed specification.

Where additional controls are used for monographed stocks, evidence should be provided to show that these are met.

Stability of Stocks

Evidence of stability should be provided unless stocks are freshly prepared for immediate use.

The stability of homeopathic stocks should be established with due reference to the specification used to control the stock at the time of preparation.

Stability should be monitored over an appropriate time period in controlled conditions and a suitable shelf-life established, for example two years. This work may be carried out on an on-going basis, and applicants may apply to extend the shelf-life in the light of available information.

Manufacturers of stocks should provide clear advice concerning storage conditions, for example, “Do not store above 25°C”, “Protect from light”.

Diluted stocks should be assigned the same shelf-life (expiry date) as the original stock.

Justification of the Homeopathic Nature of the Stock

Reference should be made to a suitable Materia Medica such as Clarke or Bœricke. Where a stock has not been included in a Materia Medica, appropriate literature references should be provided.

Production and Control of the Dosage Form

- A manufacturing and control file for each pharmaceutical form.
- A description of the method of dilution and potentisation.

Where the diluted homeopathic stock is to be added to a base, for example a cream, ointment or pillule, details of the manufacture of that formulation must be provided. If the information you are giving relates to a number of remedies that are produced by one company, please provide the information in the form of a formulation master file.

The quality standards applied to homeopathic medicines are similar to those applied to allopathic medicinal remedies. The special nature of homeopathic remedies is such that where manufacturing processes for dosage forms are standardised, the supporting data on the formulation can be held in a master file to which the applicants may cross refer. Due to the extremely low levels of stocks present in the dosage form, it is particularly important to ensure that adequate planning and in-process control is applied to the manufacturing process in order to ensure batch to batch homogeneity.

Formulation Master Files

Applicants may choose to present data on 'inert' or 'un-medicated' dosage forms (for example lactose tablets or dilution fluids) in the form of a formulation master file to which they may cross-refer following its approval.

The Formulation Master File should contain the following information:

* Formulation details
* Development pharmaceutics
* Container to be used for marketing
* Method of manufacture, in-process controls, including application of the diluted stocks
* Specification for the inert or un-medicated dosage form
* Batch data for the inert or un-medicated dosage form
* Stability data for the inert or un-medicated dosage form

Complete composition
Full details of the formulation should be provided including the theoretical composition of excipients in the final formulation.

Development pharmaceutics
Details should be provided of any development work which is relevant to the formulation such as preservative efficacy data for topical creams, oral liquids, eye drops and multi-dose injections.

Container
A brief description of the container and closure should be provided.

Manufacture
Applicants should refer to the method set out in a named homeopathic pharmacopoeia, and should provide supplementary information as set out below. Applicants will be expected to comply with good manufacturing practice requirements (Directive 91/412/EEC, http://ec.europa.eu/health/files/eudralex/vol-5/dir_1991_412/dir_1991_412_en.pdf) and take account of any special requirements for the production of homeopathic remedies (as set out in the Annex to the '*Orange Guide' to Good Manufacturing Practice*, http://www.mhra.gov.uk/Publications/Regulatoryguidance/Medicines/CON2030291). The following information should be included:

Batch size and manufacturing formula
Details of a typical batch size should be provided.

The quantity of stock to be added to the dosage form and the degree of dilution of the stock prior to it being added should be declared.

The manufacturing process
The key elements of the manufacturing process and any standard operating procedures used should be summarised.

Details should be provided of all measures taken to avoid cross-contamination. Any sterilisation procedures should be described.

In-process controls
Where in-process controls are used, for example during the dilution process, these should be stated.

Process validation
Information on process validation should be made available, particularly with regard to more sophisticated dosage forms. For sterile remedies (eye drops, intramammary remedies and injections) an accepted pharmacopoeial method of sterilisation should be used.

Specifications
Specifications should be provided for raw materials and stocks.

Specifications of excipients to be used in the un-medicated dosage form should be declared.

Container and closure specifications (size and shape) should be listed, and details should be provided of the materials used in their construction.

Finished Product Specification
The FPS should control the organoleptic and physical characteristics of the remedy. Where possible an identity test should be included for the stock at low dilutions.

The FPS should take account of any special characteristics of the dosage form. For example, assay limits are required for preservatives, and sterility tests are required for remedies such as eye drops, intramammary remedies and injections.

Analytical Controls
All methods used should be pharmacopoeial (e.g. British Pharmacopoeia (BP), Ph. Eur.). Where a method is not appropriate, a suitable, validated alternative should be used.

Batch Data
Batch data should be made available for at least three consecutive batches which should preferably be production batches.

Dilution and Potentisation
Details of the homeopathic method used for dilution and potentisation should be provided, together with the method used to incorporate the diluted stock into the inert dosage form. Validation data should be provided to demonstrate that this process is uniform.

The quality and quantity of diluent should be described, and details of any in-process controls provided.

Stability Studies
Stability studies should be carried out on at least two batches of the remedy stored for at least six months in the container for marketing and should be conducted at a defined temperature or range of temperatures. The results should justify the proposed shelf life of the remedy. The extent to which stability studies are carried out will require careful consideration, and will depend upon the nature of the remedy. Examples of what might be required include preservative efficacy data for creams, or maintenance of alcohol content for oral liquids.

For parenteral preparations supplied in multi-dose containers in-use stability data should be provided. The purpose of such testing is to establish a period of time during which the remedy may be used following the removal of the first dose of remedy from the container without adversely affecting the integrity of the remedy. Further information on the data required can be found in the *CVMP's Note for Guidance, 'In-use Stability Testing of Veterinary Medicinal Products' (EMEA/CVMP 127/95).*

The stability of tablets or granules medicated using high dilutions of stock can be established and the results extrapolated to other tablets, provided an identical container and manufacturing process are used.

For more complex dosage forms such as creams, intramammary remedies, injections or multidose eyedrops, stability should be evaluated for individual formulations.

Stability of the Dosage Form

- Data concerning the stability of the remedy.

Stability testing of the dosage form is necessary to ensure that the finished product specifications are met throughout the claimed shelf life. This includes evidence to show that the dosage form remains stable over the claimed shelf life at a specified temperature.

Registration by Other European Economic Area (EEA) States

A copy of any registrations or authorisations obtained for the same remedy in other EEA states, including the number of the relevant ManA and all other supporting data submitted to that MS. (The EEA comprises the EU MS plus Iceland, Liechtenstein and Norway).

Registration by the Medicines & Healthcare Products Regulatory Authority (MHRA)

A copy of any certificates of registration granted by the MHRA for the human version of the remedy under the equivalent human scheme, including all the supporting data submitted to the MHRA.

If you are applying to register a homeopathic remedy for veterinary use that is already registered under the equivalent human scheme, you will need to provide the VMD with all the details that you submitted to the MHRA, together with your completed application form and a copy of the MHRA's registration. There are a number of small differences between the two schemes which you may need to take into consideration when applying to the VMD. In conjunction with the dosage regime, you will need to identify the target species on either the label and/or sales presentation that you submit for each remedy.

Labelling

A specimen or mock-up of the outer packaging and immediate packaging of the remedy to be registered. You should use the dummy code Vh 9999/9999 on your mock-up or specimen label.

Biological Substance

In the case of a remedy containing biological substances, a description of the measures taken to ensure the absence of pathogens.

Withdrawal Period

It is necessary to detail the proposed withdrawal period necessary to ensure that the provisions of Regulation 470/2009 are complied with together with all necessary justification. This Regulations is available on http://ec.europa.eu/health/files/eudralex/vol-5/reg_2009-470/reg_470_2009_en.pdf

Commission Regulation EU No 37/2010 – is a list of all substances permitted to be used in food producing animals with the maximum residue limit (MRL) values (if required) in Table 1 and a list of substances not permitted for use in food producing animals in table 2. This Regulation is available on http://www.vmd.defra.gov.uk/public/vmr_legislation.aspx

Applications for Remedies Already Registered Elsewhere in the EEA

If you are applying to register a homeopathic remedy for veterinary use that is already registered elsewhere in the EEA, you will need to provide the VMD with all the details that you submitted in your application to the original MS, together with a copy of the certificate of registration. You will additionally need to submit all the requisite details to the VMD in English.

List of Abbreviations

AE	Adverse Event
AVM-GSL	Authorised Veterinary Medicine – General Sales List
BP	British Pharmacopoeia
CMS	Concerned Member State
DCP	Decentralised Procedure
Defra	Department for Environment, Food & Rural Affairs
EC	European Commission
EEA	European Economic Area
EMA	The European Medicines Agency
EU	European Union
FPS	Finished Product Specification
HMA	Heads of Medicines Agency
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
ManA	Manufacturing Authorisation
MRL	Maximum Residue Limit
MRP	Mutual Recognition Procedure
MS	Member State
Ph. Eur.	European Pharmacopoeia
POM-V	Prescription Only Medicine – Veterinarian
QRD	Quality Review of Document
RMS	Reference Member State
VHR	Veterinary Homeopathic Remedy
VMD	Veterinary Medicines Directorate
VMGN	Veterinary Medicines Guidance Note
VMP	Veterinary Medicinal Product
VMR	Veterinary Medicines Regulations

VETERINARY MEDICINES GUIDANCE NOTE

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