



Veterinary Medicines
Guidance Note

Animal Test Certificates

No 8

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ASSURING THE SAFETY, QUALITY AND EFFICACY
OF VETERINARY MEDICINES



THESE NOTES ARE ONLY A GENERAL GUIDE AND MUST NOT BE TREATED AS A COMPLETE OR AUTHORITATIVE STATEMENT OF THE LAW ON ANY PARTICULAR CASE

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INVESTOR IN PEOPLE

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INTRODUCTION

1. This is one of a series of Guidance Notes explaining requirements under the Veterinary Medicines Regulations ('the Regulations'). The Regulations are revoked and replaced every year, so the references to them should be read as referring to the ones that are currently in force. Therefore, the date and number of the Statutory Instrument is not shown in this Guidance Note. The Guidance Notes will be updated as necessary and the date of the most recent update is shown on the front cover. The Regulations set out the UK controls on veterinary medicines, including their manufacture, advertising, marketing, supply and administration. The purpose of this note is to provide guidance on the UK's Animal Test Certificate (ATC) scheme.
2. Although this VMG Note attempts to cover most issues that are likely to arise in connection with putting together applications for an ATC, we recognise that it is not exhaustive. If you would like further advice in respect of a specific problem concerning an application please telephone the relevant assessors for advice or Licensing Administration to organise a meeting. Contact details are available on our website, www.vmd.gov.uk.
3. The aims of the Veterinary Medicines Directorate (VMD) in the authorisation process in respect of ATCs are:
 - to provide appropriate safeguards for those animals involved in tests and trials;
 - to provide adequate safeguards for those people administering the product (users), people who may consume product from treated animals (consumers) and the environment;
 - encourage trials and tests to be carried out in the UK by providing a positive environment for research and a rapid system of approval for applications to conduct clinical trials of veterinary medicinal products in animals.
4. Please note that guidance is provided in this document for both pharmaceutical and immunological applications. Some parts of the guidance, however, are only relevant to one type of application and these are noted as such.

BACKGROUND

5. In order to develop new veterinary medicines and add new target species and/or indications to existing ones, it is necessary to test medicines in animals. At some, usually early, stages of the product development, a licence issued by the Home Office under the Animals (Scientific Procedures) Act 1986 (A(SP)A) will be needed. Further information is available from the Home Office website <http://www.homeoffice.gov.uk/science-research/animal-testing> (tel 0207 035 5545).

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6. The Veterinary Medicines Regulations control other tests and trials of medicines, in particular those undertaken in client-owned animals under field conditions, where an investigating veterinarian acts in accordance with “recognised veterinary practice” and the Veterinary Surgeons Act. Examples include trials conducted by pharmaceutical companies to generate the necessary data to support a future application for a Marketing Authorisation (MA) and small scale trials conducted by veterinarians involved in research.
7. Veterinary surgeons on their own initiative may carry out some types of trials without further authority, for example, a veterinary surgeon may try out various treatments in order to determine the best one for particular cases. Such trials or investigations in which veterinary medicinal products (VMPs) are administered in accordance with their Summary of Product Characteristics¹ (i.e. authorised species, indications, dose regimen etc), or in which the decision to treat individual animals (or groups of animals on the same holding) is made in accordance with the provisions of the “cascade” as stated in the VMRs, do not require further authority
8. However, for other types of trials investigating VMPs, an Animal Test Certificate (ATC) is required.
9. Due to the investigational nature of an ATC, no charge should be levied for the trial material. However, in exceptional circumstances, and subject to the prior agreement of the VMD, it may be possible to charge a fee to recover the cost of the trial.

GENERAL GUIDANCE

10. Generally ATCs will be applied for by pharmaceutical companies wishing to generate data for MAs (Type “A” or Type “B”). However, veterinary surgeons can apply for an ATC for a product, in order to conduct clinical trials to advance knowledge in a particular area. These types of trials may be eligible for the simplified Type “S” application. Please see paragraph 30 for further clarification of the different ATC types.
11. The VMD will evaluate applications looking particularly at the risks involved in the proposed trials. Our main concerns will be for safety, especially to consumers of produce from the treated animals, to the environment, to people using the product or handling treated animals, and to the animals undergoing the trial.
12. An ATC authorises both the trial itself and the procurement and supply of the veterinary medicine used in it. Therefore, the applicant will need to describe the proposed trial and justify the use of live animals. As trials by their nature will cover only a limited number of animals on a small number of sites, data are not necessary to demonstrate quality, safety and efficacy to the level required in

¹ SPCs are published on the VMD’s website: www.vmd.gov.uk/espcsite/default.aspx

support of an application for an MA. The submission of a full data dossier is not required.

13. Applicants should ensure that the procedures and techniques used during the field trials, including sampling, use of placebos and control animals, comply with recognised veterinary practice (see RCVS Guide to Professional Conduct – Interface between the VSA and A(SP)A). As detailed in paragraph 27, placebos can be included within an ATC providing use does not compromise animal welfare. The ATC itself does not relieve the veterinary surgeon from providing normal veterinary care for the animal involved in a trial. Should this be prohibited by the protocol of the trial, the Home Office should be consulted regarding the need for an ASPA licence.
14. Studies intended to generate data for a marketing authorisation application should be carried out in accordance with the VICH guideline: Good Clinical Practice (GCP, implemented in July 2001). The VMD will not approve test protocols, except to ensure that safety and welfare issues are adequately addressed. It is for applicants to ensure that the results of trials carried out under ATCs will be appropriate for any subsequent applications for an MA.
15. It should be noted that a target species tolerance study conducted under an ATC should normally be conducted at the proposed dosage, administered for the proposed duration of administration. Target species tolerance studies involving either multiple dosages or an extended dosage period would normally require a licence under A(SP)A.
16. In the interests of animal welfare, a justification is required for the proposed trial. Reference to laboratory or target animal efficacy or challenge studies may be necessary.
17. To avoid unnecessary delay in the processing of the application, applicants should not submit data that are not required in the application form.
18. The ATC may be issued for a single batch of a product for which data solely relating to this batch are provided. Alternatively, it may be issued on the basis of agreed specifications so that different batches of product may be used in the trial.
19. It is not a requirement that products used in ATC trials be manufactured under GMP conditions, although this is encouraged.
20. At the approval of the ATC S trial, a note outlining the study may be published on the VMD website. The note will contain information on the purpose of the study, species, class of product and details of the site where the study will be conducted.

RETURN OF ANIMALS TO THE FOOD CHAIN

21. Where an A(SP)A trial is also in part a medicinal test in animals which the applicant wishes to be returned into the food chain, this would normally require an

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ATC in addition to an A(SP)A project licence. If you are considering such a course of action, you should consult the VMD in the first instance, to establish whether or not the trial is eligible for consideration under the ATC scheme. ATCs for A(SP)A trials are classified as Type A, B or S as in paragraph 30 below, depending on the nature of the material to be administered and the protocol of the trial.

IMPORT OF A MEDICINAL PRODUCT

22. The holder of an animal test certificate may import anything specified in the animal test certificate in accordance with the conditions in that certificate.

CONSULTATION WITH DEFRA AND OTHER GOVERNMENT DEPARTMENTS

23. Because the Importation of Animal Pathogens Order 1980 may also apply, VMD will consult Defra's Animal Health and Welfare Directorate when applications are received relating to agents that are:

- exotic to the UK;
- notifiable;
- zoonotic; or
- may affect statutory or non-statutory surveillance for animal disease.

24. The VMD considers issues of safety to the consumer as part of the assessment. Nevertheless, we may consult other government bodies including the Food Standard Agency (FSA) in relation to food safety, should the need arise. We advise the FSA routinely of all ATC applications for food producing species and send copies of the dossiers to them. We would normally expect to conduct any such consultations within the usual assessment timescale.

25. For applications involving veterinary medicinal products containing or consisting of genetically modified organisms (GMOs) the applicant should contact the VMD for advice. Any medicinal trial in animals involving the deliberate release of GMOs into the environment requires both an ATC and a Part B Experimental Release Licence, which is issued by the GM Policy Unit of Defra under Directive 2001/18/EC. The part B experimental release licence is required before a trial may start.

APPLICATION FOR AN ATC

26. In general, each individual trial requires an ATC as the purpose of the trial should be to generate data in respect of one therapeutic indication and should normally involve a single species of animal. Possible exceptions to this rule would be trials of ectoparasiticides, endectocides or multivalent vaccines. This is because there might be concurrent infestations/infections of more than one species of pathogen/parasite in the same animal and more than one indication would be tested. Individual trials may be multi-centred.

27. A trial may involve more than one product but only where:
- the second product to be administered is a placebo or a positive control which is authorised for that species and indication in an EU Member State. In exceptional circumstances, a human authorised product may be used as a control product where use is well supported by literature references and there is no suitable authorised VMP; or
 - the products are of the same pharmaceutical form and contain the same ingredient(s) but differ in the strengths or dosages of the active or inactive ingredient(s); or
 - for vaccines, the products differ only in the inclusion or exclusion of particular antigens under investigation; or
 - the products are of two or more dilutions of either the same allergen extract or mixture of allergen extracts used for desensitisation therapy; or the products used for *in vivo* diagnosis of allergy are manufactured by the same method from closely related substances (e.g. pollen); or
 - more than one product is expected to be required to produce therapeutic efficacy, e.g. herbal medicines, sedative/analgesic combinations, allergens.
28. Each trial requires a separate application form, trial protocol and product literature, plus supporting data as appropriate.

TSE COMPLIANCE

29. For Type B ATC applications only, it will be necessary to demonstrate compliance with the latest version of the joint Committee for Proprietary (Human) Medicinal Products/Committee for Veterinary Medicinal Products (CPMP/CVMP) guideline on “Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products”, EMEA/410/01. The relevant information which should accompany each application consists of a signed declaration in the appropriate format together with a Certificate of Suitability demonstrating compliance with the relevant monograph or the relevant scientific data where appropriate. The formats and the declarations are available on the VMD website.

ATC APPLICATION TYPES

30. In order to minimise the data requirements and time to approval of simple applications, ATCs are divided into three types (“A”, “B” and “S”) depending on their complexity. The application forms and supporting documentation reflect this.
31. For all trials which are primarily intended to generate pivotal data for a **future marketing authorisation application**, the application must be for either a Type A or Type B ATC, according to Table 1 below:

Table 1 Type A or Type B?

1.	Is the product already authorised as a human or veterinary medicinal product in an EU member state?	Yes → Q. 2	No → Type B
2.	Is the product an immunological/biological product? Is the product a pharmaceutical product?	Yes → Q. 3 Yes → Q. 4	
3.	Is the trial to be conducted in the species included on the existing MA?	Yes → Type A	No → Type B
4.	Is the trial to be conducted in companion animals only?	Yes → Type A	No → Q. 5
5.	Is the trial to be conducted in the authorised food species at the same or a lower dose rate and using the same method of administration?	Yes → Type A	No → Type B

32. For **small scale trials conducted by veterinary surgeons as clinical research** the type of ATC required will be either A, B or S, according to Tables 2 and 3 below. Type S ATCs are intended for research trials which do not need to be conducted in accordance with GCP and involve small numbers of animals.
33. Type S trials should not enrol more than 50 animals to the investigatory product treatment group, unless this is clearly justified by statistical aspects of the study design.
34. Type S trials will not normally involve immunological products, owing to the inherent risks of such products being contaminated with extraneous agents. It is advisable to approach the VMD to discuss an application for a Type S ATC for an immunological/biological product, unless it already has a Marketing Authorisation in the EU. Products used in Type S trials should usually be used without alteration; where any alteration is proposed (for example dilution) product quality and hence safety must not be compromised.
35. Researchers are encouraged to contact Marketing Authorisation Holders of authorised VMPs prior to undertaking Type S trials with their products.

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Table 2: Pharmaceutical products to be tested in:

- **Companion animals**
- **Horses declared never to enter the food chain**
- **Other (including food species) animals which have been declared never to enter the food chain²**

Is the product:			
An EU (incl. UK) authorised VMP?		Go to Q. 1	
An EU (incl. UK) authorised Human product?		Go to Q. 4	
A VMP or Human product authorised in one of the named third countries?		Go to Q. 5	
None of the above, e.g. a new chemical entity?		Type B	
EU (incl. UK) authorised VMPs			
1.	Is the product to be used in the authorised species?	Yes → Q.2	No → Q. 3
2.	Is the product to be used at the authorised (or lower) dosage regimen which is supported by published literature ³ of the <u>efficacy</u> of the active substance in this species for the proposed indications?	Yes Type S	No → Q. 3
3.	Is there published literature supporting the <u>target species safety</u> , and <u>efficacy</u> of the active substance in this species, for the proposed indications and at the proposed dose regimen?	Yes Type S	No Type A
EU (incl. UK) authorised Human products			
4.	Is there published literature supporting the <u>target species safety</u> , and <u>efficacy</u> of the active substance in this species, for the proposed indications at the proposed dose regimen?	Yes Type S	No Type A
VMPs and Human products authorised in third countries			
5.	Is the product authorised in one of the following countries: US, CA, JP, NZ, AU?	Yes → Q.6	No Type B
6.	Is the product authorised for the same species and indications, using the same dosage regimen? (i.e. VMPs only)	Yes Type S	No → Q. 7
7.	Is there published literature supporting the <u>target species safety</u> and <u>efficacy</u> of the active substance in this species for the proposed indications and at the proposed dose regimen?	Yes Type S	No Type B

² To include zoo animals.

³ Refer to Annex A, Notes on supporting data for Type S applications.

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Table 3: Pharmaceutical products to be tested in food species

Is the product:			
1.	A human or veterinary medicinal product authorised in the EU (incl. UK)?	Yes → Q.2	No Type B
2.	Is the product a VMP to be used in the authorised species, at the same or a lower dose rate, observing the withdrawal periods in the SPC?	Yes → Q.5	No → Q. 3
3.	Are the pharmacologically active substances in the product listed in Annex I, II or III of Regulation (EC) 2377/90, and statutory withdrawal periods are to be applied? ⁴	Yes → Q.6	No → Q. 4
4.	Is the product to be used for the treatment of horses, <u>and</u> the active substances are listed as “essential for the treatment of equidae” according to Regulation (EC) 1950/2006 <u>and</u> a 6-month withdrawal period is to be applied?	Yes → Q.6	No Type B
5.	Is there published literature ⁵ to support the <u>efficacy</u> of the active substance in this species for the proposed indications?	Yes Type S	No → Type A
6.	Is there published literature ⁵ to support the <u>target species safety</u> , and <u>efficacy</u> of the active substance in this species, for the proposed indications and at the proposed dose regimen?	Yes Type S	No Type B

HOW TO APPLY

36. Four copies of the application form for each proposed trial should be completed, in English, and returned to the VMD at the address at the end of this note. If there is insufficient space on the form, additional pages should be included. Each copy should be signed by the applicant or a person authorised to do so on behalf of the applicant or in the case of a corporate body, by a proper officer and be accompanied by the supporting information referred to in the application form. The application forms are available on the VMD’s website, under Industry Information > Applications Page. Wherever possible, the application should also be supplied in a suitable electronic form to submissions@vmd.defra.gsi.gov.uk.
37. Applications submitted as hard copy should be bound in a ring binder or some other form of secure and semi-permanent binding with pages numbered consecutively by volume. There should be no more than 350 pages in any one secure binder.

⁴ For statutory withdrawal periods, refer to the Veterinary Medicines Regulations 2007, Schedule 4. The VMD reserves the right to specify an appropriate withdrawal period.

⁵ Refer to Annex A, Notes on supporting data for Type S applications.

38. An applicant may make precise cross-reference to relevant studies in the data dossier for an authorised product which is held by the VMD and to which the applicant has a right to access.
39. The supporting data for the different application types are set out in the application forms. Detailed notes are provided in respect of the supporting data for Type B and Type S applications for pharmaceutical products in Annex A.

HOW THE VMD HANDLES APPLICATIONS

40. On receipt of an application the VMD will check that it is complete. The target for validation and informing the applicant of the outcome is 5 calendar days from receipt of the application. The VMD may seek to clarify minor issues by telephone or e-mail to help speed up the validation process.

TYPE A AND TYPE S

41. The target for processing Type A and Type S application is within 30 calendar days after receipt of a valid application. There is no provision for stopping the clock on a Type A or Type S application.
42. Provided that applicants have submitted the correct information in the appropriate format and proposed suitable product literature, the need for additional questions should arise only rarely. If questions arise during the assessment process these should generally be put to the applicant by Day 15. The applicant will then have 10 days in which to respond or the application will be considered withdrawn. There will then be a further 5 days to grant or refuse the certificate.
43. If the applicant fails to respond to the questions within the 10 day target and still wishes to carry out the test they must reapply including the responses to the earlier questions in their revised application. A further fee and a second 30 calendar day time period will usually apply in such cases.
44. We will aim to resolve outstanding issues and inform the applicant by e-mail of the final decision on whether or not to grant a certificate before Day 30. If an applicant has not received written questions about the application by Day 15, the ATC will have been accepted. A Certificate will be granted and the applicant should receive the formal documentation in the post shortly thereafter. The Certificate will include the conditions under which it has been granted.

TYPE B

45. The target for processing a Type B application is within 50 calendar days after receipt of a valid application. There is provision for stopping the clock where necessary.
46. The VMD will keep all requests for additional data to the minimum. In cases where more data are required the assessor for each discipline will usually send

an individual question list to the applicant, to avoid delay and expedite responses. However, clocks will only be stopped when all aspects of the application have had an initial assessment.

47. A deadline will be set for the provision of responses. This will normally be 3 months. If the required responses are not received by the specified deadline then the application is considered to have been withdrawn, unless a revised deadline has been agreed with the VMD. Applicants will formally be notified of the outcome of Type B applications as appropriate as soon as a final decision has been made.

FURTHER CONSULTATION

48. After validation of all applications, consideration will be given as to whether additional scientific advice is required. This may be necessary in relation to products containing new active chemical entities not previously approved in the EU or, in the case of vaccines, live antigens not previously included in a UK authorised product. Although we will aim to do this within the time scale set out in the previous paragraphs, this may not always be possible as it depends on the dates of committee meetings.
49. If a Type B application is to be refused you will be offered the opportunity to appeal and the procedure will be explained to you.

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50. The terms and conditions of the authorised ATC comprise:
 - all information submitted with the application;
 - additional documents detailing any changes or additions made during the assessment period; and
 - any general or special conditions imposed by the VMD.
51. Any alterations in the trial which bring it outside of the terms and conditions of the ATC, will be a breach of the terms and conditions on which the ATC is granted. In such circumstances, either a variation or a fresh ATC should be obtained. A person carrying out a medicinal test on animals which is not covered by the terms and conditions of an ATC is liable to prosecution. The holder of an animal test certificate is guilty of an offence if he supplies a product for administration that is not within the terms of the animal test certificate

OBLIGATIONS OF ATC HOLDERS

52. The issuing of an ATC gives authority for the holder to supply and use the product in accordance with the approved dossier. In particular, the ATC holder must observe any special conditions written into the ATC, use the approved product literature and comply with the laws relating to variations. By signing the application form the applicant undertakes:

- to meet the terms and conditions of the ATC;
 - to ensure that Informed Owner Consent is obtained for off-label or unauthorised use of products used in the trial.
 - to ensure that all procedures conducted under the ATC comply with the RCVS Guide to professional conduct and “recognised veterinary practice” (Guide to professional conduct, Part 3, Annex b, A(SP)A and VSA interface, www.rcvs.org.uk). For Type S ATCs, the researcher/investigator and at least two other veterinary surgeons, who are independent of the trial and have a further qualification in the discipline concerned, should provide signed confirmation that they have reviewed the protocol and that they are satisfied that the study is ethical and to be conducted in accordance with these requirements.
 - to notify the VMD of any other information affecting the safety of the product used; and
 - to notify the VMD of any discontinuation of the test and the reasons for it.
53. An ATC may be revoked (or, if appropriate, compulsorily varied - this does not apply to Type S ATCs) if:
- the ATC holder fails to observe any of the terms and conditions of the ATC;
 - doubts arise about the safety or quality of the product;
 - changes in the conduct of the test have an adverse effect on the safety of target or other animals, of consumers of the produce of target animals, of users of the product or of the environment;
 - information supplied at the time of application is found to have been deficient or incorrect in a material way (i.e. in a way which influenced the VMD's decision).

PHARMACOVIGILANCE

54. It is a condition of any ATC that any serious suspected adverse reaction (i.e. any reaction involving a human or which has caused increased mortality or serious ill-health in treated animals) to any test substance authorised by means of an ATC (i.e. test article, control or placebo) must be reported to the VMD within 15 days.
55. For suspected adverse reactions, which are not serious, holders should keep appropriate records. A summary of all suspected adverse reactions experienced will be required if the ATC is to be renewed. The normal obligations apply to reporting of suspected adverse reactions to UK authorised products used within the terms of their authorisation as positive controls within trials. Applicants should refer to VMG Note 13 for guidance on pharmacovigilance.

56. A suitably qualified person, usually a veterinary surgeon, must have overall responsibility for investigating any suspected adverse reactions, monitoring them and, if necessary, reporting them to the VMD. Appropriate arrangements should be put in place to ensure that 'blinding' of products does not interfere with pharmacovigilance responsibilities.

LABELLING OF PRODUCTS SUPPLIED UNDER AN ATC

57. An ATC imposes conditions regarding labelling. These conditions require that the containers and outer packages of products must be labelled clearly and indelibly in accordance with the general labelling rules for products with MAs. For small containers, alternative words should be discussed with the VMD. Where trials are being conducted according to a blind design, these rules will be relaxed to the extent necessary to allow for this. A package leaflet is required if there is insufficient space on the label to include all relevant text. For Type A and B ATCs, label and package leaflet text should be submitted for approval, and the approved labels and package leaflet must be used for the trial. For Type S ATCs, the applicant will be required to submit a statement of user and target species safety warnings to appear on the label/leaflet, but otherwise it is the responsibility of the ATC holder to ensure that the labelling/leaflets conform to requirements. Additional guidance on the warnings can be found in Annex 1 of the Type S application form.
58. As a general rule the VMD will expect labels to contain the following minimum information in English:
- the words "For Veterinary Clinical Trial Use Only";
 - name or other designation of the product;
 - quantity of product;
 - any restrictions on use;
 - expiry date and, if appropriate, in-use expiry date;
 - directions for use specific to the trial including dosage, frequency, duration, method and route of administration;
 - contra-indications, warnings and precautions, and special instructions for handling and storing the product;
 - instructions for disposal (in most cases, these should state that any unused product and containers should be returned to the trial sponsor);
 - if to be used in species used to produce food (including horses, rabbits and pigeons) either the specified withdrawal period or the words "Not to be Used in Animals for Human Consumption";
 - name and address of ATC holder and ATC number;
 - the manufacturer's batch number;

- a unique code/number identifying the individual container, where appropriate (e.g. where the identity of the products used in the trial are blinded).
59. For authorised veterinary medicinal products, the approved labelling may be used, providing it is in English, but a small overlabel should indicate any amended directions/warnings, the ATC number and the words “Veterinary Clinical Trial Use Only” to ensure accountability in line with GCP requirements.
60. If any of the above is likely to cause difficulties, particularly in respect of blind trials, please contact the VMD for guidance.
61. There are suggested proformas for the labelling of materials to be used in a clinical trial on the VMD website www.vmd.gov.uk/General/AppsPage/proforma.pdf. You will need to adapt these as appropriate to take account of the nature of individual studies.

VARIATIONS

62. Due to the costs involved, it will not be possible to vary a Type S ATC. Minor changes may be made by prior agreement and notification to the VMD. More substantial changes will require a new application.
63. Applications for variations to Type A and B ATCs should set out and justify the proposed change. Two copies of the application should be sent to the VMD. Only the types of changes listed below may be dealt with by way of a variation application:
- the name of the product or the designation by which it is known;
 - name and address of the ATC holder;
 - the name and address of any person in the UK taking part, in the course of a business carried on by him, in the manufacture or assembly of the product and for imported products, the name and address of the manufacturer and assembler of the product in the form imported;
 - a justified increase in the number of animals to be treated with the test product;
 - the inclusion and/or exclusion criteria used in the selection of animals for the test, or the withdrawal of animals from the test;
 - the arrangements for monitoring safety including any instructions, restrictions or precautions to ensure the safety in use and at disposal;
 - the name or qualifications of the overall Monitor of the trials (see VICH guideline on Good Clinical Practice for definition of Monitor);
 - the name of the site Investigator involved in the animal test (see VICH guideline on Good Clinical Practice for definition of Investigator);

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- the name of any additional Investigator and addresses of any additional test sites;
 - product shelf-life;
 - the approved label text.
64. Variation applications will be processed within 30 calendar days after receipt of a valid application. The processing period will be divided into 15 days for initial assessment and sending out any questions, 10 days for the applicant to respond and the final 5 days for the assessment to be concluded. The applicant will be informed by e-mail whether the application has been approved or refused and the formal documentation will follow in the post. If refused, a further application will be necessary in which the reasons for refusal should be fully addressed.
65. It is recognised that some tests cannot be set up until an outbreak of a particular disease of interest occurs. In these circumstances an ATC may be issued for a maximum number of sites and animals with the condition that test sites and the exact number of animals included at each site are advised as they become known. There will be no specific charge for this.
66. All other changes require new ATC applications. However, where an existing UK trial is being modified, as long as the product formula, species and purpose of the trial remain the same, a Type A procedure and fee will apply.

DURATION AND RENEWAL OF ATCS

67. An ATC remains in force for a maximum period of two years. In most circumstances it is expected that the authorised trial will have been completed within that period. If the trial is still in progress a Type A or B ATC may be renewed on application.
68. Applications for renewal should include particulars of the ATC and of any variations previously made to it, particulars of the progress of the trial, and a summary account of suspected adverse reactions noted. A justification for the renewal must be given.
69. For Type S ATCs, the applicant must notify the VMD of a request for an extension. A report documenting the reasons and justification for the request and a summary account of suspected adverse reactions must be provided. One extension would be permitted, subject to receipt of a satisfactory report.

FEES

70. The VMD is required to recover the costs of its licensing work by means of fees charged for applications. Details on the relevant fees can be found in the Veterinary Medicines Regulations, which are available on the VMD website.
71. The fee should not accompany the application and nor should it be paid in advance of the submission of the application. Instead, on receipt of a valid application, the VMD will send an invoice to the applicant for the correct amount.

FURTHER INFORMATION

72. 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.gov.uk).

ANNEX A

**Notes on Supporting Data
for Type B and Type S
Applications for
Pharmaceutical
Products**

SUPPORTING DATA FOR TYPE B APPLICATIONS

The data requirements for an ATC are detailed on the application form. If data are not available for all areas, this will not necessarily mean that an ATC will not be granted but a justification for the absence of data should be provided in every case. The VMD reserves the right to request additional data to that listed in this annex for the assessment of safety of the product, including those aspects of quality that may impact on safety.

The following notes are provided for Type B applications for pharmaceutical products to supplement the information on the application form:

QUALITY

Qualitative and Quantitative Particulars

The product should be described (colour, shape, dimensions, pharmaceutical form).

A very brief rationale for the selection of the formula for use in the trial should be presented. Any similarities of the proposed trial material with an already authorised product (e.g. same unconventional excipient) should be mentioned.

If a positive control is to be modified for double blinding purposes, information on the nature of the modification should be given together with a consideration of whether the modification has an impact on bioavailability. This may also be relevant for some Type A applications.

Method of Preparation of the Final Product

For non-standard manufacturing processes, a detailed description of critical steps should be provided.

Process validation data are NOT required.

Specification of the Active Substance

For those active substances which are confirmed in the table in section 4.6 of the application form as complying with either the Ph.Eur, BP, or the pharmacopoeia of another EU member state, USP, or the USNF, further information is not generally required. However, where additional controls need to be applied to the active substance due to the nature of the dosage form and method of manufacture (e.g. sterility, particle size) these should be provided.

For those active substances, which do not fall into the categories mentioned above, the active substance specification should be summarised and justified. The summary should indicate each of the tests, the limits applied and the type of test method (e.g. assay, 98.5 - 101.0%, HPLC). Alternatively, a copy of the Certificate of Analysis for

the batch used to manufacture the trial material should be supplied together with a justification demonstrating the suitability of the batch for the intended use.

Active Substance Manufacture, Evidence of Structure and Impurities

Additional data are required for novel molecules and for active substances from a source not currently authorised for use in the manufacture of veterinary or human medicines in the EU. Novel molecules in this case are considered to be those substances which have not previously been used in the EU in/on animals or humans.

The additional data which are required are:

- The method of manufacture of the active substance should be summarised. Any substance of animal origin used in the manufacture of the active substance should be clearly identified and their suitability for use in the manufacturing process, in terms of product safety, should be discussed.
- For non-pharmacopoeial active substances, evidence of structure data should be presented together with interpretations.
- Information on the potential impurities of the active substance, their origin and the levels actually observed in batches of the active substance should be presented. Their significance in terms of the safety of the product to be tested should be commented upon.

Control of other ingredients

For ingredients that do not comply with either the Ph.Eur, BP, or the pharmacopoeia of another EU member state, USP or USNF, specifications should be provided. The specifications should include test and limits and an outline of the method, eg GC.

If a single batch approval ATC is required, for those ingredients not covered by any of the pharmacopoeias listed above, a Certificate of Analysis should be provided. A justification demonstrating the suitability of the material for the intended use should accompany the Certificate of Analysis.

Release Finished Product Specification

Complete analytical methods do not need to be presented. Supporting validation data should NOT be supplied.

An end of shelf-life Finished Product Specification is NOT required.

If a single batch approval is sought, rather than summarising the Finished Product Specification in section 4.10 of the application form, a copy of the Certificate of Analysis of the batch of product intended for use in the trial should be provided.

If a placebo product is to be used in the trial, you should also supply a simple Finished Product Specification for the placebo. The Specification should primarily cover

physical characteristics, e.g. appearance, dimensions, fill weight/volume and absence of the active substance.

Stability and shelf-life

A shelf-life, and, if appropriate in-use shelf-life linked to specified storage conditions, should be proposed and justified. Stability data (chemical and physical) for the proposed formulation should be presented in the form of tabulated results. Stability data on closely related formulations (e.g. different strengths of the proposed dosage form containing the same excipients) may be acceptable with a justification for the use of such data. Similarly stability data on the same formulation stored in similar packs (e.g. same contact materials but different shapes/sizes) would require a justification.

Although provision of stability data on pilot batches stored under Committee for Medicinal Products for Veterinary Use (CVMP) recommended conditions is desirable, provision of stability data for laboratory batches stored for example under ambient conditions may be permitted depending on the nature of the proposed trial.

The requirements for stability data will depend on the type of product under investigation and the proposed trial. It is acceptable to provide only sufficient data to support a short shelf life, e.g. 3 months, if this is adequate for the purpose of the trial. For trials involving extended periods of time, either more stability data will need to be provided. Alternatively, subject to there being a reasonable expectation of good stability based on related formulations, an agreement may be reached on real-time monitoring of stability during the course of the trial.

HUMAN SAFETY

General

As indicated previously, summary data only are required. The amount of detail to be included depends on the authorisation status of the product or its active substances. Some examples are shown below as a guide, and the application form itself provides further information.

Product containing an active substance authorised for use in another species: an MRL summary report (if available) could be provided, supplemented with any additional data appropriate to the trial, a user risk assessment and a detailed summary of relevant residues depletion data together with a proposal for a withdrawal period.

Product containing an active substance used in products other than veterinary medicines, e.g. in pesticides: a summary of a published pesticide assessment, supplemented with any additional data appropriate to veterinary medicines, a user risk assessment and, if relevant, a detailed summary of residues depletion data together with a proposal for a withdrawal period.

Product containing a completely new active substance: detailed tabulated or descriptive summary of each study, together with conclusions on user and consumer warnings.

Tabulated summaries may usefully be provided in the formats defined for the safety expert reports which must accompany applications for marketing authorisations.

User Safety

A user risk assessment must be submitted for all applications. This should include a summary of the product's basic toxicity and a consideration of the likely user exposure during the trial.

Consumer Safety

If produce from animals treated during the trial is to enter the food chain, the data provided must demonstrate that the food will contain no harmful veterinary drug residues. Where the pharmacologically active substance of the products to be used appears in Annex I, II or III of Regulation 2377/90 applicants will need to propose a suitable withdrawal period. As an alternative to the presentation of residue depletion studies and depending on the nature of the substance concerned, a relevant withdrawal period may be proposed and justified by the submission of reasoned arguments. Relevant withdrawal periods are at least: 28 days for meat, 7 days for milk and eggs or 500 degree days for fish. Where other pharmacologically active substances are concerned, applicants will need to justify an MRL and withdrawal period.

In exceptional circumstances, applicants may wish to start field trials before sufficient information is available to allow a full assessment of residues. In this case produce from the treated animals may not enter the food chain and applicants must agree to label the product "*Not to be used in Animals for Human Consumption.*" The applicant must justify this approach and state how treated animals are to be disposed of to ensure that their products do not enter the food chain.

ENVIRONMENTAL SAFETY

An environmental risk assessment is NOT required for Type B ATC's for companion animals. Completion of sections 1, 2 and 3 of the application form is all that is required.

It is not expected that there will be significant exposure of the environment as a result of the use of a product under an ATC. This is mainly due to the small scale of use, regardless of whether an existing product or a new product is used.

Applicants should provide an environmental risk assessment which demonstrates that environmental exposure to the test product is not extensive. In most cases information on the number of animals on the trial, the number of sites and the dose and duration of treatment will be sufficient to show that exposure will not be significant. The applicant

should also consider any other information or environmental risk assessment available for the test product which might be of relevance when preparing their assessment.

In exceptional cases, exposure of the environment may be found to be significant. In these cases a summary report of individual fate and effects studies available should be provided with the risk assessment. These summaries should be sufficient, for the ATC application, but the assessor may ask for a full report of one or more studies, if necessary, to complete the environmental risk assessment.

TARGET SAFETY SPECIES

The VMD will need to be sure that safety in the target species is acceptable, at the proposed dosage and for the proposed duration of administration, and that there is a reasonable margin of safety. Additionally, animal welfare needs must be considered.

For example provision must be made for:

- alternative treatment if the product under trial is not efficacious or if unacceptable side effects are observed;
- the blinding code to be broken if necessary, for example, if an animal has a suspected adverse reaction and the trialist needs to know whether it has been given the test product, a positive control or a placebo;
- treatment of any animal which has had a placebo administered to it, if treatment is required.
- Availability of normal 24-hour per day emergency service for veterinary care and appropriate arrangements. This is particularly relevant if this service is delegated, for continuity of care and for the blinding code to be broken in the event of an emergency.

The proposed numbers of animals that the test product is to be administered to must be justified and based on statistical requirements and must be the minimum number consistent with the objective.

A suitably qualified person, usually a veterinary surgeon, must be available to investigate any suspected adverse reactions, treat the animal(s) appropriately and, if necessary, remove it (them) from the trial. This is normally the trial Monitor (see VICH on Good Clinical Practices for definition of Monitor).

EFFICACY DATA

The objective of the proposed trial should be outlined and justified. Evidence should be provided to indicate that there is a reasonable expectation that the test product will produce the desired effect. For example, reference to laboratory and/or pilot studies may be necessary.

TRIAL PROTOCOL

Trial protocols should be GCP compliant. Whilst the protocol should be submitted to the VMD, the VMD will not approve it. It is for applicants to ensure that the results of trials carried out under ATCs will be appropriate for subsequent applications for marketing authorisations, and that accurate records are maintained for company archives.

SUPPORTING DATA FOR TYPE S APPLICATIONS

Target Species Safety and Efficacy data

Scientific literature should be presented. Ideally, the literature should be derived from publications in peer-reviewed journals but alternative sources may be taken into consideration, for example, papers presented at conferences which have been reviewed by a committee. Other data (e.g. specialist group email discussion lists) may also be taken into consideration, but will be judged on merit. The literature should provide supportive evidence for the safety and efficacy of the active substance, when used in accordance with the proposed dosage regimen, in the target species.

If there is an existing EU authorisation for the product in the same species and using the same dosing regimen, target species safety data are not required.

For an “exotic” species, it may be possible to present literature from a related species if its relevance can be justified by the applicant.

VETERINARY MEDICINES GUIDANCE NOTE

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OF VETERINARY MEDICINES