APPENDIX B
to VPC(88)108

GUIDANCE NOTES FOR THE REVIEW OF VETERINARY PRODUCTS CONTAINING HORMONES

1.1 Data should be presented in accordance with EC Directives 81/851 and 81/852 on Veterinary Medicinal Products: paragraph 11 and Parts II to VIII of the MAFF guidance document "Notes on Applications for Product Licences for Veterinary Medicinal Products" (MAL 10) which is available on request from the licensing authority at Tolworth Tower. Guidance notes on the data requirements for residues are also attached. The following notes should also be taken into account.

1.2 Acceptable maximum residue limits for hormones have not been established, applicants must propose withdrawal periods which should be determined from appropriate toxicology data:-

a) A range or toxicology studies should be carried out to determine no effect levels including no hormonal effect levels in suitably sensitive species. Histology may need to be carried out on hormone sensitive target organs. (Will 90 day studies be required?).

b) Residue depletion data will be required from use of the product as recommended in each target species and residue assays performed on a full range of tissues including milk where appropriate.

c) Metabolism data will be required and data on residues of metabolites if appropriate. It should not be assumed that bound residues are metabolically inactive unless this has been proven by studies submitted.

d) Validated assay methods of sufficient sensitivity must be used and the animal's endogenous hormones taken into account in terms of cross reactivity.

e) Information will be required on whether the active ingredient or its metabolites are absorbed from the gut where appropriate.

f) Data will be required to show that there is a lack of carcinogenic hazard both to consumers of produce from treated animals and to operators. A range of appropriate mutagenicity tests must be carried out and life span studies may be required. Natural steroid hormones are not genotoxic but do have tumourigenic effects and potential hazards to consumers must be addressed. Relevant literature may be utilised. In the absence of data, comment must be provided on why such data are not required.

g) It might be useful to present data showing that the concentrations of active ingredient and metabolites at the proposed withdrawal periods are no greater than endogenous concentrations, following correct usage of the product.

h) Although residues in meat and milk may be very low following use of the product, the significance of these residues should be assessed.

An adequate safety margin must be applied between the residues without hormonal effect in suitably sensitive species and the levels of exposure of human beings to residues from treated animals.

i) Application of standard withholding periods (28 days tissues; 7 days milk) may be considered by the Veterinary Products Committee if data to support the proposed withholding periods are incomplete or absent UNLESS the Committee has reason to think that these may not be appropriate. Applicants should argue their case as to why such periods could be applicable. [Do the Committee agree this and can they provide advice for guidance to applicants as to which type of product this will be of particular relevance).

1.3 Efficacy data from published sources on the active ingredient will generally be acceptable but an adequate review of it must be provided and it must be capable of providing clear evidence for supporting the proposed dose of the product. The relevance of literature or studies provided must be justified where these refer to a salt other than that included in the product. The salt form could affect the physical properties of the steroid (e.g. particle size, solubility etc) and thus the activity.

For applications for products used in non-food producing animals extensive controlled efficacy trials as described in paragraph 1.5 may not be necessary if other data are adequate.

1.4 Justification of the formulation and the proposed dose must be provided.

1.5 The range of indications proposed must be strictly supported by the evidence provided. Efficacy data should be provided from use of the proposed product as recommended and statistical analyses carried out. Such efficacy data should be provided from a range of UK animal husbandry conditions and the nutritional status of animals recorded as this may also affect the results.

1.6 It is known that the duration of action of hormones and the onset of action can vary considerably depending on structure and route of administration. Data on metabolism and biological half life must be provided.

1.7 In relation to implant products:-

a) In-vivo release data will be required in an adequate number of animals.

b) Residue data will be required covering the full length of the claimed efficacy and to support the proposed withdrawal periods.

c) Withdrawal periods must be stated from the removal of the implant.

d) Data will be required from trial work on the recovery of implants from treated animals.

1.8 Target species tolerance data from the use of the product at the maximum recommended dose in each indicated species must be provided and must address the full duration of treatment proposed.

1.9 Applicants should provide with each application a brief section containing the following information in the format of a suspect adverse reaction Type A report which is:-

a) Product name

b) Product licence number

c) Period of report-(preferably the last 5 years of marketing)

From: To:

d) Number of doses sold in period specified at (c)

e) Number of suspected adverse reactions recorded at (c) for each animal species

f) Number of deaths at (e) for each animal species

g) Brief general description of reactions recorded.

Where efficacy trials using the proposed product are provided applicants must comment on the occurrence of any adverse reactions, especially injection site reactions.

1.10 For those active constituents which are derived from natural sources full information will be required on the manufacture, purification, isolation and control of the substance. In particular, the country of origin of the material from which the substance is derived must be stated and a full account given of the measures followed to ensure that the substance is free from pathogenic contamination.

1.11 Product licences issued after the implementation of EC Directives 81/851/EEC and 81/852/EEC will not need to be reviewed fully. It will be necessary to ensure that the data supplied in support of the safety of the product meets current requirements. In particular it will be necessary to ensure that the data are sufficient to give assurances that the withdrawal periods are acceptable and the product literature is acceptable.

As there are no established maximum residue limits for hormones, companies holding such product licences will be requested under section 44(2) of the Medicines Act to provide the following information to the Medicine Unit:-

1) A summary of the data on which current withdrawal periods are based, with adequate reference to the full data at which the full results can be seen.

2) Current product literature for the product.

3) A type A report as described at paragraph 1.6 above.

Following receipt of the above information, consideration will be given as to whether full data will be required.

GUIDANCE ON DATA REQUIREMENTS FOR RESIDUES

1. a) The data required and their assessment will be the same for products subject to formal review as for applications for product licences or variations to existing product licences.

   b) Companies should submit all the pertinent residue data available to them, together with a formal statement that this has been done.

2. a) Appropriate residue data must be available, unless it can be clearly established that there is no systemic absorption.

   b) Residue data should be provided for each food producing species for which recommendations for use are made.

   Specific residue data will be required for each species of poultry or fish for which claims are made.

   c) If pharmacokinetic data adequately demonstrates equivalence with another species for which there are full residue data, then detailed information may not be required for the second species. For example, data from a ruminant is more likely to be appropriate for another ruminant species, than a non-ruminant.

   d) Data on each edible tissue of importance should be submitted unless, with a justification, the 'worst case' residue target tissue (e.g. liver) only is submitted. It is then assumed that all edible tissues carry the same residue profile.

   The important edible tissues are, skeletal muscle, fat, liver, kidney and also milk and eggs. As a general principle, because of consumption habits, poultry (and possibly pigs) should provide skin plus fat instead of fat alone. Subcutaneous or carcase fat is preferred for residue determination, rather than abdominal fat. Data from poultry kidney tissue are not required.

   e) Data on residues found at the injection site are required, particularly when the product is a depot-type administration. Information on the lack of residues at any injection site at the end of the withholding period would be particularly useful. Justification should be provided to ensure that the sample assayed is representative of the amount of tissue likely to be consumed.

3. a) A sufficiently large number of animals should be used so that the withholding period can be reliably calculated. This depends on the variation of residues in individual test animals and on the extent that the test animals are representative of animals in the field.

   b) For cattle, sheep, pigs - pharmacokinetic data (plasma profiles) should be provided from at least 6 animals. Additionally, individual results on residues from at least 4 mature animals (i.e. ruminating calves or lambs, or weaned pigs) per observation should be available.

c) For the horse - individual results from a minimum of 3 animals will be adequate, provided there is sufficient supportive pharmacokinetic argument. Such data will not be required if the product is contra-indicated for use in equines intended for human consumption.

d) For each poultry or fish species - the above minimum criteria apply, but applicants would be expected to provide results from a larger group of animals.

4. a) Experimental data, which should include both the parent compound and metabolites of biological significance should be presented from each individual, with calculated means. Observations should be made with adequate frequency for example, before, during, and after treatment. These should be maintained until well after an acceptable residue concentration is attained, so as to show that there is no resurgence of activity.

b) Separate residue data must be obtained following each recommended route of administration and formulation. The dose used must be the maximum recommended and given for the full period of administration shown in the proposed data sheet. If it can be adequately demonstrated that a residue plateau is reached within a shorter period of administration, then residue data from that time point may be provided.

c) Residue data on any toxicologically significant 'Other Ingredients' should be provied in addition to data from 'Active Ingredients'.

5. a) Residue assay methods should be validated for the particular tissue involved and the quantitative limits of sensitivity for the parent compound and its metabolites provided.

b) It is an advantage that tissue samples are taken for residue purposes, before, at and after the proposed withholding period. Such samples should be retained under suitable storage conditions so that assays can be repeated some time after the initial examination, if necessary.

6. The calculation of withholding periods should be based on the achievement of a residue tolerance taking into account the ADI calculated from the 'no effect level' (nel) and using appropriate safety factors. Residue tolerances laid down by the Codex Alimentarius (JECFA), the CVMP and the VPC etc should be taken into account.

7. For antimicrobial products, the minimum inhibitory concentrations in a range of appropriate micro-organisms, should be considered when establishing a residue tolerance which is without risk to consumers.

For non-antimicrobials and anti-microbials which might exhibit toxicological activity, the results from a sub-chronic oral study in the most sensitive species, is used to establish a nel. Frequently rats are used in 90 or perhaps 28 day studies. However, other tests (e.g. teratology study), routes (e.g. where appropriate inhalation) or