

V.P.C. (88)139

COMMERCIAL IN CONFIDENCE

Medicines Act - Veterinary Products Committee

Review of Veterinary Medicines Containing Hormones

1. The review of veterinary medicines containing hormones is shortly to be announced. At the July meetings members were asked to provide written comments to the Medicines Unit on VPC(88)108, which contained a list of products that would be included in the review and draft proposed guidance notes to be sent to applicants.
2. Officials have now checked for correctness the list of products included in this review. Revised guidance notes to be sent to applicants are attached.
3. It is the intention of the Licensing Authority to issue review call-up letters and guidance notes to licence holders in October 1988.
4. Members are asked to agree the attached guidance notes which will be sent to applicants for this review.

September 1988

MEDICINES UNIT  
VLA 8575  
GCE/AKG/JOBDistributionTo the Veterinary Products Committee )  
To the Scientific Secretariat Committee ) for action

## 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. The general guidance notes on the data requirements for residues which have been provided for every review so far are also attached. The following notes should also be taken into account.
- 1.2 Acceptable maximum residue limits for hormones have not yet been established, and applicants must propose withdrawal periods which should be determined from appropriate toxicology data:-
- a) Data will be required to show that there is a lack of carcinogenic hazard both to consumers of produce from treated animals and to users of the product. A comprehensive range of appropriate mutagenicity tests must be carried out and life span carcinogenicity studies may be required. Some natural steroid hormones are not genotoxic but may have tumourigenic effects and potential hazards must be addressed. Relevant literature may be utilised. In the absence of data, justification must be provided on why such data are not presented.
  - b) Metabolism data will be required and data on residues of metabolites as appropriate. It should not be assumed that bound residues are metabolically inactive unless this has been proven.
  - c) Information will be required on bioavailability and pharmacokinetics in the target species.
  - d) A range of appropriate toxicology studies should be carried out to determine no effect levels including no hormonal effect levels in suitably sensitive species. Histology will need to be carried out on hormone sensitive target organs.
  - e) Validated assay methods of sufficient specificity and sensitivity must be used and the animal's endogenous hormone levels taken into account in terms of cross reactivity.
  - f) 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. A sufficiently large number of animals should be used in residue studies so that the withholding period can be reliably calculated.
  - g) Although residues in meat and milk may be very low following use of the product, the significance of these residues must 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. The potential for absorption of the active ingredient or metabolites from the human digestive tract could be addressed.

- h) The calculation of withholding periods should be based on the achievement of a residue tolerance taking into account the ADI (Acceptable Daily Intake) calculated from appropriate studies and using appropriate safety factors. The safety factor to be used would depend on the information available on metabolism and toxicology. x100 might be appropriate for compounds with no significant toxic potential. x1000 or greater might be appropriate for compounds with greater toxic potential or where full information on metabolism is not available. When calculating a tissue residue tolerance applicants should in their calculations take account of average human bodyweight, as well as daily dietary intake of meat, offal and fat, and when calculating a milk residue tolerance, take account of daily dietary intake of milk.
- 1.3 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.
- 1.4 Information should be provided on the effects of the product on the animal's endogenous hormone production.
- 1.5 Justification of the formulation, the proposed dose and route of administration must be provided.
- 1.6 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 in the target species. 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 active ingredient (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 1.7 may not be necessary if other data are adequate.
- 1.7 The range of indications proposed must be fully supported by the evidence provided. Efficacy data should be provided from use of the proposed product as recommended in each target species 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.

1.8 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) Where appropriate, withdrawal periods must be stated from the removal of the implant.
- d) Data will be required from trial work on the efficiency of recovery of implants from treated animals.

1.9 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.

1.10 Applicants should address operator safety and include safety warnings in product literature where appropriate e.g. use of impervious gloves and coveralls.

1.11 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, including injection site reactions.

1.12 For those 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. It should also be noted that

substances derived from glandular extracts or serum intended for treatment of ruminants or pigs require authorisation under the Serum and Glandular Products Order, and account should be taken of any risk of contamination with B.S.E.

1.13 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 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. In addition comment or argument is required to assure the Licensing Authority that the proposed withdrawal periods would be satisfactory, even though this information may have been previously provided at the time the original product licence application was considered.
- 2) Current product literature for the product.
- 3) A type A report as described at paragraph 1.11 above.

Following receipt of the above information, consideration will be given as to whether further 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 carcass 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 provided 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

longer dosing periods (e.g. chronic life span studies) may give a lower  
nel and should be used in calculation of acceptable residues, ADIs and  
withholding periods.

3 These are general considerations and for particular situations, it is  
advisable to discuss test protocol designs and the evaluation of  
results, in consultation with professional staff at the Medicines Unit,  
CVL Weybridge.

Revise 1  
April 1988



## Checklist of items to include in reviewed licence applications

This list is not intended to provide a complete list of all information required in support of licence applications. It does, however, identify the main sections to be included in any dossier. Failure to supply information or provide a satisfactory argument as to why such data are not included under each heading will constitute grounds for refusing to accept an application.

- I. General information (eg. name of product etc).
- II. Information on physico chemical, biological or microbiological tests
  - Summary and expert report
  - Qualitative and quantitative composition
  - Method of preparation
  - Control of starting materials
  - Control tests on intermediate products (if appropriate)
  - Control tests on finished product
  - Stability tests
- III. Toxicological and Pharmacological tests
  - Summary and expert report
  - Single dose toxicity
  - Toxicity with repeated administration
  - Target species tolerance
  - Foetal toxicity
  - Fertility studies
  - Pharmacodynamics
  - Pharmacokinetics
  - Determination of residues if appropriate
  - Effects of residues
  - Systemic absorption of products for topical use
- IV. Clinical trials
  - Summary and expert report
  - Clinical reports of individual and collective trials
  - Side effects etc
- V. Experiences in man if appropriate including any known adverse effects
- VI. Special particulars
  - Dosage form
- VII. Details of suspected adverse reactions reported to the company over the previous five years