ANNEX 4

MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Note

This annex applies to all veterinary medicinal products falling within the scope of Directive 81/851/EEC other than immunological veterinary medicinal products, which are the subject of a separate annex.

Manufacture of premixes for medicated feedingstuffs

For the purposes of these paragraphs,

— *a medicated feedingstuff* is any mixture of a veterinary medicinal product or products and feed or feeds which is ready prepared for marketing and intended to be fed to animals without further processing because of its curative or preventative properties or other properties as a medicinal product covered by Article 1(2) of Directive 65/65/EEC;

— *a pre-mix for medicated feedingstuffs* is any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feedingstuffs.

1. The manufacture of premixes for medicated feedingstuffs requires the use of large quantities of vegetable matter which is likely to attract insects and rodents. Premises should be designed, equipped and operated to minimise this risk (point 3.4.) and should also be subject to a regular pest control programme.

2. Because of the large volume of dust generated during the production of bulk material for premixes, specific attention should be given to the need to avoid cross contamination and facilitate cleaning (point 3.14), for example through the installation of sealed transport systems and dust extraction, whenever possible. The installation of such systems does not, however, eliminate the need for regular cleaning of production areas.

3. Parts of the process likely to have a significant adverse influence on the stability of the active ingredient(s) (e.g. use of steam in pellet manufacture) should be carried out in an uniform manner from batch to batch.

4. Consideration should be given to undertake the manufacture of premixes in dedicated areas which, if at all possible, do not form part of a main manufacturing plant. Alternatively, such dedicated areas should be surrounded by a buffer zone in order to minimise the risk of contamination of other manufacturing areas.

Manufacture of ectoparasiticides

5. In derogation from point 3.6, ectoparasiticides for external application to animals, which are veterinary medicinal products, and subject to marketing authorisation, may be produced and filled on a campaign basis in pesticide specific areas. However other categories of veterinary medicinal products should not be produced in such areas.

6. Adequate validated cleaning procedures should be employed to prevent cross contamination, and steps should be taken to ensure the secure storage of the veterinary medicinal product in accordance with the guide.

Manufacture of veterinary medicinal products containing penicillins

7. The use of penicillins in veterinary medicine does not present the same risks of hypersensitivity in animals as in humans. Although incidents of hypersensitivity have been recorded in horses and dogs, there are other materials which are toxic to certain species, e.g. the ionophore antibiotics in horses. Although desirable, the requirements that such products be manufactured in dedicated, self-contained facilities (point 3.6) may be dispensed with in the case of facilities dedicated to the manufacture of veterinary medicinal products only. However, all necessary measures should be taken to avoid cross contamination and any risk to operator safety in accordance with the guide. In such circumstances, penicillin-containing products should be manufactured on a campaign basis and should be followed by appropriate, validated decontamination and cleaning procedures.

Retention of samples (point 1.4 viii and point 6.14)

8. It is recognised that because of the large volume of certain veterinary medicinal products in their final packaging, in particular premixes, it may not be feasible for manufacturers to retain samples from each batch in its final packaging. However, manufacturers should ensure that sufficient representative samples of each batch are retained and stored in accordance with the guide.

9. In all cases, the container used for storage should be composed of the same material as the market primary container in which the product is marketed.

Sterile veterinary medicinal products

10. Where this has been accepted by the competent authorities, terminally sterilised veterinary medicinal products may be manufactured in a clean area of a lower grade than the grade required in the annex on “Sterile preparations”, but at least in a grade D environment.