European Medicines Agency
Veterinary Medicines and Inspections

Revision 1[1]

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PENICILLINS

SUMMARY REPORT

1. Penicillins (and their salts including the benzatine, procaine and sodium salts) have been widely used in veterinary medicine for more than 30 years and today form the most important group of antibiotics.

2. Penicillins have a low toxicity in the normal sense of the word; the therapeutic index is more than 100, and toxic effect have only been seen after extremely high doses. No teratogenic effects have been recorded.

   In connection with therapeutic use of penicillins hypersensitivity reactions are by far the most commonly encountered side-effects. The amount of penicillin haptene necessary to sensitize a subject is several orders of magnitude higher than the quantity needed to trigger an allergic reaction in an already sensitized individual. Furthermore, it takes a much higher oral dose to induce an allergic reaction than if the drug is administered parenterally. Against this background it can be concluded that the small amounts of penicillins which may be present in food products of animal origin are not able to sensitize the consumer, but will, at the most, trigger a reaction in already sensitized subjects. Literature contains only very few references reporting allergic reactions traceable to penicillin residues in foods. At least 6 µg penicillin (equivalent to 10 IU penicillin) seems normally necessary to provoke an allergic reaction.

   Penicillins are strong inhibitors of the bacteria used in production processes employed by the dairy industry. Concentrations as low as 0.006 µg (0.01 IU) penicillin per gram milk considerably inhibit starter cultures and delay acid production. In order to secure dairy products of acceptable quality, penicillin residues in milk must not exceed 0.003 µg (0.005 IU) per gram.

3. Penicillins are mainly excreted unchanged in urine and to a lesser extent in bile. While metabolism is considered to be of little importance in the elimination of most penicillins, the penicilloic acid metabolite is significant from a safety point of view as it is reported to be allergenic and so may play a role in hypersensitivity reactions. All penicillins are eliminated rapidly after absorption.

4. In order adequately to protect the consumer and secure dairy production, the Committee for Veterinary Medicinal Products recommends the following maximum residue levels for six penicillins:

COMPOUND	EDIBLE TISSUES µg/kg	MILK µg/kg
Benzylpenicillin	50	4
Ampicillin	50	4
Amoxicillin	50	4
Oxacillin	300	30
Cloxacillin	300	30
Dicloxacillin	300	30

[1] The summary report was updated in May 2008 when information relating to the outcome of using different analytical methods to measure the relevant marker residues came to light. At the same time, the document was updated to explain why it is acceptable to monitor only parent compound levels even though allergenic metabolites may also be present.

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5. In a review of this summary report[1] it was noted that even though the penicilloic acid metabolite is considered to be significant with regards to hypersensitivity reactions, the maximum residue limits for penicillins refer to the parent compounds only, with no control of metabolite levels either by direct measurement or through use of a calculation to take account of the ratio of marker to total residues. This is acceptable as the hypersensitivity case reports on which the above maximum residue limits are based refer to levels of the parent compound only and not to levels of allergenic metabolites. It can be assumed that the patients that were the subjects of these hypersensitivity case reports were exposed to penicillin residues at a ratio of parent compound to allergenic metabolites that is similar to that which will be experienced by consumers exposed to penicillin residues in animal derived food products. Consequently, it is concluded that as long as the level of the parent penicillin conforms to the maximum residue limit, levels of allergenic metabolites will be present at safe levels.

6. For screening of milk samples within the EU, a method using *Bac, stearothermophilus* (var. calidolactis, ATCC 10149) has been recommended. This method is especially sensitive to penicillins with detection limits for benzypenicillin, ampicillin and amoxicillin at 2(-4) µg/kg, and for oxacillin and cloxacillin 15(-35) µg/kg.

   Concerning screening of edible tissues within the EEC, there has been agreement on using the 'Four-plate-method'. The limit of detection for benzylpenicillin, ampicillin and amoxicillin is at 30-60 µg/kg and for oxacillin and cloxacillin it is at 300 µg/kg.

7. In 2008 it became clear that recorded levels of amoxicillin residues seen in residue depletion studies performed in food animals were greater when fluorescence detection was used as a method of analysis than when LCMS was used. It was concluded that, while LCMS accurately quantifies the level of the marker residue (parent compound), fluorescence detection measures the marker residue plus amoxicilloic acid, since both compounds are converted to the same fluorescent derivative. As a result, data generated in studies using fluorescence detection have led to high apparent residue levels and inaccurate conclusions with regards to the levels of marker residue present in tissues (mainly kidney and liver), i.e. fluorescence detection leads to over-conservative results. A parallel situation is likely to occur for the quantitation of the marker residue and penicilloic acids for the other penicillins named in this report. It can be concluded that LCMS is the most appropriate method for measurement of the marker residue.