



European Medicines Agency
Veterinary Medicines and Inspections

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**COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE
(CVMP)**

**REFLECTION PAPER ON ANTIMICROBIAL RESISTANCE SURVEILLANCE AS
POST-MARKETING AUTHORISATION COMMITMENT**

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INTRODUCTION (Background)

The CVMP has requested that for some centrally authorised antimicrobial products, the Marketing Authorisation Holder (MAH) carries out antimicrobial resistance monitoring as a Post-Marketing Authorisation (PMA) commitment¹. This includes regular reports to the CVMP.

The CVMP agreed to request the SAGAM to reflect on the issue of Post-Marketing Authorisation Resistance Surveillance (PMARS) as the benefits of such studies for individual marketing authorisations has been matter of discussion.

Lately, the number of resistance monitoring activities within the EU by official and private institutions has increased and it could be argued that the need for antimicrobial resistance PMA commitments regarding antimicrobial resistance surveillance is becoming less important. However most of the official monitoring programmes focus on major food producing species and zoonotic bacteria, therefore further surveillance activities might be required.

WHEN ARE POST-MARKETING AUTHORISATION COMMITMENTS TO BE REQUESTED

Post-marketing authorisation commitments could be requested in cases where the documentation provided prior to marketing authorisation could not cover all aspects of importance when assessing the risk for emergence of resistance. Such measures could include monitoring of resistance in bacterial species including target animal pathogens, food borne pathogens and/or indicator commensal organisms.

PMARS in target animal pathogens is primarily related to animal health and thus requests for such data will be for the benefit of target animals. However, the presence or emergence of acquired resistance on these bacteria may act as an early warning and thus a secondary objective for asking for such data would be related to public health.

For products intended for food producing animals, the importance of PMARS for public health purposes depends on the assessment of the exposure of animal bacteria to the active substance, of humans to resistant bacteria or resistance genes and the perceived importance of the substance to public health.

PMARS could be requested also for products intended for companion animals.

PMARS on target animal pathogens could be considered for products containing antimicrobial substances complying with the below criteria, independent of the authorisation procedure (centralised, mutual recognition, decentralised or national) and route of administration (e.g. including premixes and products administered *per os*):

1. New classes of drugs, which have never been authorised for veterinary use, i.e. substances with new mechanisms of action.
2. Substances belonging to already existing classes of antimicrobials but with extended or altered spectrum of activity (e.g. new generation cephalosporin).

A decision tree is included in the Annex to clarify those cases where, taking into account the above criteria, a PMARS could be requested.

It is important to note that the intention of such commitments is not to replace or repeat the monitoring of antimicrobial resistance in zoonotic and commensal bacteria currently undertaken by competent authorities of Member States but should comprise aspects not covered or intended to be covered by official monitoring programmes. In cases where sufficient information is available from public monitoring programmes the MAH could be asked to summarise and report such information instead of or complimentary to activities sponsored by the MAH.

¹ In accordance with Article 34 (4) (d) of Regulation (EC) No. 726/2004 of the European Parliament and of the Council

CHOICE OF METHODOLOGY TO RECOMMEND AND INFORMATION TO PROVIDE FOR SPONSORED ACTIVITIES

The bacteria to be covered should be included in a list, on a case-by-case basis, dependent on data available prior to marketing authorisation. Recommendations for PMARS sponsored by the MAH could include:

- When possible considering the prevalence of the microorganism the sample size should be sufficient to ensure that a trend in resistance can be detected with a statistical power of 80% or more.

Monitoring should be performed using validated laboratory methods and collecting correct epidemiological information, as described in VICH Topic Guideline GL27: Guidance on Pre-approval Information for Registration of New Veterinary Medicinal Products for Food Producing Animals with Respect to Antimicrobial Resistance - CVMP/VICH/644/01-FINAL.

(<http://www.emea.europa.eu/pdfs/vet/vich/064401en.pdf>)

- MIC values should be determined with a validated and controlled method, such as those described by ISO-method (BS EN ISO 20776-1:2006), if available. The definition of resistance should be agreed with the relevant regulatory authority before the start of the study.
- If resistant isolates are detected, when possible, information on the case from which the sample was taken should be gathered. This information could be used e.g. to assess whether resistance resulted in therapeutic failure.
- If isolates with resistance phenotypes not previously described are detected, their resistance mechanisms should be characterised in relation to transferability and cross and co-resistance.
- Reports to the relevant regulatory authority should be provided regularly; the duration of the commitment should be decided on a case-by-case basis. The MAH should assess all the data available and provide an overview. A brief description of the use of the product on the market, including the sales as provided for the PSURs should be provided to support the PMA resistance surveillance.

REPORTING FROM PUBLIC MONITORING ACTIVITIES IN THE EU

MAHs could be asked to provide summaries on public monitoring activities either complimentary or as an alternative to sponsored activities.

There are several resistance monitoring activities ongoing in different Member States, and the bacterial species considered usually include animal pathogens, food borne pathogens and indicator commensal organisms. According to Directive 2003/99/EC of the European Parliament and of the Council of 17 November 2003 on the monitoring of zoonoses and zoonotic agents all Member States should develop such programmes. The Directive states that Member States must implement monitoring programmes to provide comparable data on the occurrence of antimicrobial resistance in zoonotic agents and, in so far as they present a threat to public health, other agents. Specific requirements are set out in Annex II to the Directive.

Data on the occurrence of antimicrobial resistance in salmonella and campylobacter isolates from different sources (human infections, animals, foodstuffs) and indicator bacteria from the main animal species are collected and published by the European Food Safety Authority (EFSA). The reports are available at <http://www.efsa.europa.eu>.

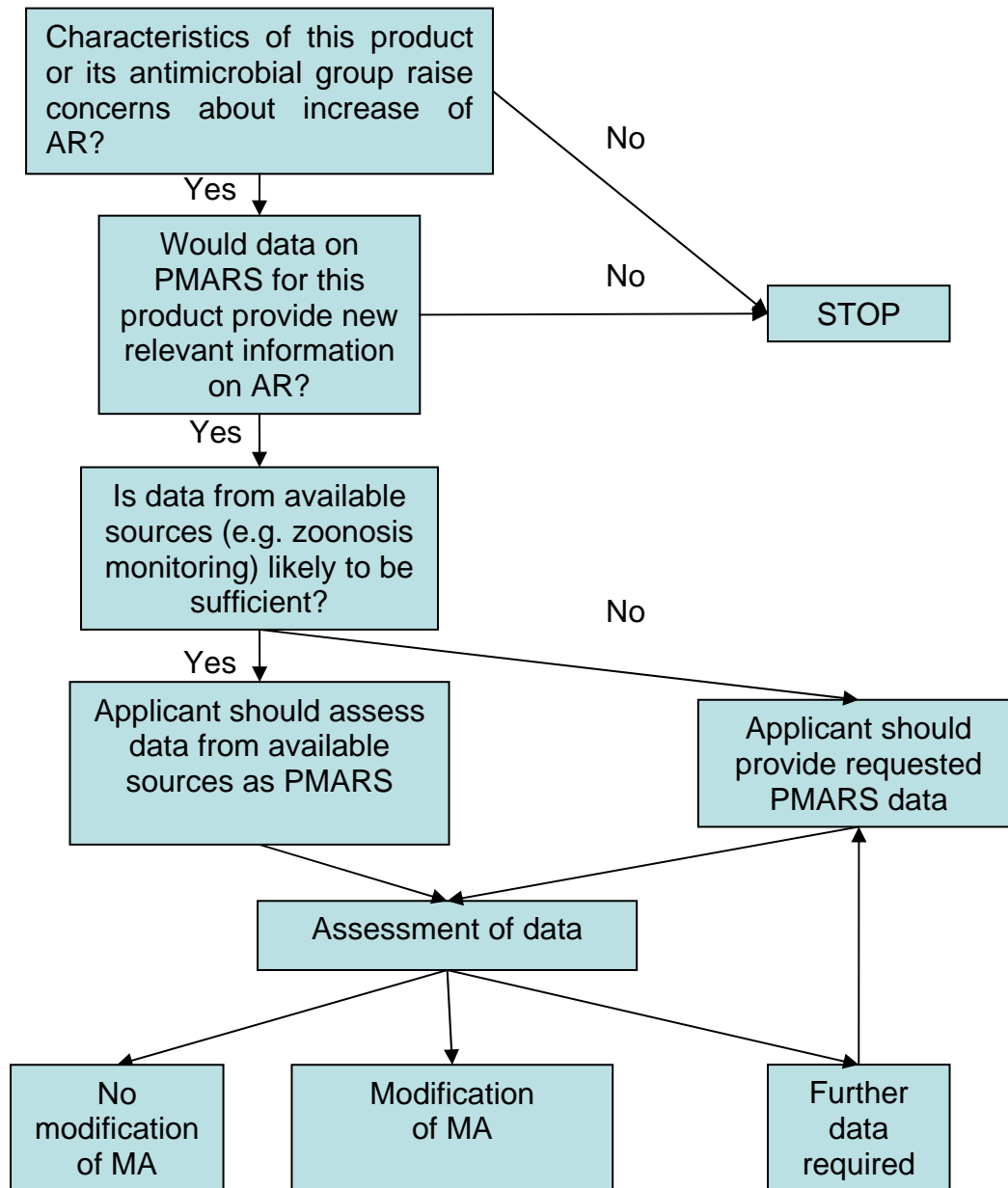
More extended data including resistance in animal pathogens are reported by the monitoring systems of several Member States, which regularly produce reports on antimicrobial resistance in bacteria of animals. A Community Reference Laboratory for antimicrobial resistance in the veterinary field has been designated by the European Commission in 2006 and Member States have designated National Reference Laboratories, to establish a European network on this matter.

CONCLUSION

- Today there are several different monitoring programmes ongoing in the EU providing useful information on animal pathogens, food borne pathogens and commensal organisms.
- Sponsored surveillance activities should be regarded as complementary to those and could be asked for under special circumstances.
- MAHs could be requested to commit themselves to discuss data available from public monitoring programmes, which are relevant for their products.
- For both sponsored surveillance activities and MAH reports from public monitoring programmes it is important that the quality of the data is high and that relevant isolates are chosen.

ANNEX

DECISION TREE



AR: Antimicrobial Resistance
PMARS: Post-Marketing Authorisation Resistance Surveillance
MA: Marketing Authorisation