European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON REFLECTION PAPER ON ANTIMICROBIAL RESISTANCE SURVEILLANCE AS POST-MARKETING AUTHORISATION COMMITMENT (EMEA/CVMP/SAGAM/428938/2007)

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	European Commission	Belgium
2	IFAH-Europe	Belgium
3	Prof. Dik Mevius (Centraal Instituut voor Dierziekte Controle)	The Netherlands

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW
European Commission (DG SANCO) DG SANCO thanks EMEA for the consultation on the above document and shares its concerns on the increasing development of antimicrobial resistance in zoonotic agents. DG SANCO would like to make, however some comments. As indicated in the reflection paper, monitoring of antimicrobial resistance is mandatory in accordance with the provisions in Directive 2003/99/EC of the European Parliament on the monitoring of zoonoses and zoonotic agents, amending Council Decision 90/424/EEC and repealing Council Directive 92/117/EEC (OJ L 325, 12.12.2003, p.31). Implementing provisions to harmonise the monitoring of antimicrobial resistance have already been introduced. Each year monitoring results from all Member States are submitted to the EFSA who analyses the trends. DG SANCO supports this complementary action as mentioned in the CVMP's conclusions. However, it is recommended that all information collected within this post-marketing authorisation commitment, as regard to antimicrobial resistance, is forwarded to the EFSA in accordance with the provisions in the Directive 2003/99/EC. This would guarantee that all information is made available for analysis of trends as already foreseen in the monitoring Directive 2003/99/EC. DG SANCO welcomes possible recommendations form EMEA as regards requirements for the monitoring of antimicrobial resistance within the frame of Directive 2003/99/EC, where appropriate. Furthermore, DG SANCO believes that the results of the assessment of post-marketing authorisation measures on antimicrobial resistance surveillance should be discussed jointly by EMEA, EFSA and COM (DG SANCO and ENTR). Finally, DG SANCO would welcome very much that EMEA considers the providing of information on the use of the antimicrobials per species of food producing animals or, if not possible, on the sale of antimicrobials for food producing or all animals as additional post-marketing authorisation commitment. The need for such information has been highlighted in several EFSA opinions. This information would complement the information collected within the frame of Directive 2003/99/EC and would allow to better assess the link between the use of certain antimicrobials and the prevalence of resistant strains in food and food producing animals. CVMP comments The EMEA (or relevant regulatory body) could forward information on Post-Marketing Authorisation Resistance Surveillance (PMARS) to EFSA and the European Commission when considered required by the CVMP (or relevant regulatory body); this information will be treated as confidential. It has been clarified in the Reflection Paper that the use and sales of antimicrobials should be discussed as part of the PMARS.

GENERAL COMMENTS - OVERVIEW

IFAH-Europe comments

General comments

The CVMP has cited it's authority to request "for some centrally authorised antimicrobial products…antimicrobial resistance monitoring as a post-authorization commitment". However, by issuance of the Reflection paper, it is apparent that additional input is needed by all stakeholders to determine the benefits, risks and value of implementing a Post-Marketing Authorization Resistance Surveillance (PMARS) program.

Post-authorization surveillance seems to be viewed by CVMP as a pharmacovigilance (PV) activity and thus should more appropriately be considered within that context. However, as there are no adverse events that have ever been connected to the use of any veterinary medicinal product, with respect to antibiotic resistance, the proposal for PMARS by MAHs and the resulting modification of the Marketing Authorization (MA), now makes the detection of antibiotic resistance a reportable, and hence, adverse event, under PV. This has serious repercussions and implications at many levels. In addition, this would take PV from an area that receives unsolicited reports of clinical events, with the responsibility of signal detection, trending and reporting, to a level of a microbiological research group that is creating data that most probably will not have clinical relevance but could result in unwarranted labelling changes, restrictions, etc., not to mention the cost of resources to support such an effort.

Related to the need for MAHs to conduct PMARS, there will be an appearance of a Conflict of Interest should these studies be done by individual Marketing Authorization Holders (MAHs). It was for situations like this that the OIE proposed in 1999 and put into the Terrestrial Code, guidance for conducting antimicrobial resistance monitoring programs by national authorities.

CVMP comments

PMARS should not be considered as part of pharmacovigilance. Antimicrobial resistance is not included under pharmacovigilance. Lack of clinical efficacy is part of pharmacovigilance, this lack of efficacy might be linked to resistance, but in those cases those are unexpected events whilst the PMARS are scheduled reports.

GENERAL COMMENTS - OVERVIEW

IFAH-Europe comments

National and industry-led resistance monitoring programs

IFAH-Europe has long supported PMARS by national authorities, which are considered impartial with regard to the conduct of the study, analysis and communication. Although the *Centre Européen d'Etudes pour la Santé Animale* (CEESA) conducts a pan-European resistance surveillance program (veterinary, zoonotic and commensal bacteria from cattle, swine and poultry), funded entirely by the research-based veterinary pharmaceutical industry group, the data is presented at international meetings and in peer-reviewed papers only after extensive analysis to ensure a science-based report. It should be stressed yet again that the data obtained in the industry-led monitoring programs is not dissimilar to that obtained by various national monitoring programs. As such, the Industry-led programs supplement the national monitoring programs.

The need for MAHs to initiate yet more monitoring programs is thus not justified in any shape or form for MAHs involved in the CEESA program or other industry-led programs. This is a key point that requires much "reflection" in terms of the economic impact for MAHs and the potential effect on discouraging the introduction of new antimicrobial products.

CVMP comments

As indicated on the reflection paper, any available data from e.g. CEESA that would fulfil the CVMP requirements would be considered, so in many cases there will no new requirements to the MAHs, the Reflection Paper also indicates "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."

The reflection paper has been modified to reinforce that non-official sources of surveillance will also be taken into account.

GENERAL COMMENTS - OVERVIEW

IFAH-Europe comments

Industry-led surveillance programs fulfil the need for PMARS

IFAH-Europe takes the position that this Reflection paper and the proposal as it stands now, would result in a redundancy of effort by MAHs and national authorities, particularly when similar products or antimicrobial classes are considered. Since part of the industry, through CEESA, already works together to generate susceptibility data which effectively is what this proposal is requesting, it is not clear why individual companies will need to implement their own programs. This appears to be a waste of resources and duplication of efforts, both for the MAH and investigators of national monitoring programs.

Therefore, IFAH-Europe would propose to encourage and recognize the ongoing monitoring programs (like the CEESA and GERMVET programs) of those MAH that have taken and will continue to take their responsibility as an equal alternative to the PMARS proposed in the reflection paper. If the MAH subscribes to CEESA or national monitoring programs, this should suffice to fulfil the requirement of post-marketing resistance monitoring. If the MAH would choose not to participate, PMARS as suggested by the reflection paper could be imposed.

CVMP comments

See above

IFAH-Europe comments

A 'molecule approach'

The reflection paper appears to be primarily directed at pioneering MAHs (see lines 55-60) and not to be applicable to generic companies. However antibiotic resistance monitoring must be seen as a long term product stewardship responsibility and when generic MAHs appear they cannot be exempt from conducting or participating in resistance monitoring programs. Therefore it seems appropriate to advocate a "molecule approach".

When a post-MA commitment is judged to be necessary, it must be requested equally to all MAHs possessing the affected product(s), irrespective of the legal basis for the MA. Article 13 of the veterinary Directive only gives derogation from providing a full data package for the purposes of a MA application. Once in the market place all MAHs have equal responsibility for additional data requests, including PMA commitments.

CVMP approach

See the criteria for requesting PMARS for clarification on which cases the PMARS are likely to be requested.

GENERAL COMMENTS - OVERVIEW

IFAH-Europe comments

Country specific data or regional data

In case data are requested from one country, it would be very valuable to use experiences from other countries provided that similar conditions apply. Is it allowed to refer to lead compounds reflecting an entire class? Hence, a sentence such as below could be considered to include:
"*It should be ensured that resistance data from other EU countries are accepted and specifically not for each country and each product and each target animal in all countries resistance data are necessary."*
It should be stressed here that where country specific data is not available, it would be reasonable to extrapolate susceptibility data from neighbouring EU countries provided that the antibiotic susceptibility data from all available EU countries is comparable. If such comparable data is available it seems unreasonable and disproportionate to ask MAHs to conduct antibiotic susceptibility testing from target pathogens for each and every EU country in which the MAH has approval.

The principle and the conclusions of the reflection paper are acceptable. However, the reflection paper is approached from a very general point of view leaving the door wide open to many interpretations. The microbiology studies that the MA holder will undertake will have to generate information of higher quantity, quality and variety than what is performed by national reference laboratories.

CVMP comments

In those rare occasions when those studies will be requested, the CVMP does not foresee that data from all Member States should be provided but a comparable sample from representative countries (see text of the guideline on efficacy of antimicrobials (EMEA/CVMP/627/01-FINAL)).

This is a time limited defined committeemen intended to supplement the data provided with the MA in very specific cases. As above, see the criteria for requesting PMARS for clarification on which cases the PMARS are likely to be requested.

GENERAL COMMENTS - OVERVIEW

IFAH-Europe comments

Technical Comments

The possibility of an imposition of a more general and regular PMA monitoring and reporting program is also questioned for the following technical reasons:

- Interpretation of the data collected will be difficult in some instances because of the possibility of cross-resistance and/or co-selection by virtue of linked antimicrobial resistance (AMR) to related or other classes of antibiotics. Cross resistance between compounds may develop as a result of usage of other related compounds rather than the "new" compound currently being screened. The identification of linked resistance and its source is often difficult but will at least necessitate screening of all isolates against other compounds which may include competitor products and/or human products.

CVMP comment

The CVMP agrees with the comment made, however is still important to assess as far as possible antimicrobial resistance from the use of veterinary medicinal products.

- Many isolates collected by MAHs will rely on diagnostic laboratories where many referred bacterial disease cases are animals with chronic disease, often with a history of treatment with several antibiotic classes before final sampling. Use of multiple antibiotics will produce a confusing picture which often cannot be interpreted, particularly because the true history is often not readily imparted by the owner. Few MAHs will be able to set up screening which is consistently reliant on sampling new/fresh cases at farm level.

CVMP comment

PMARS are expected to use similar conditions as those described in programs above mentioned, similar problems will be encountered, however it should be possible to extract useful information.

- Although it is stated that "If resistant isolates are detected the clinical origin of the sample should be determined....." this will not be possible retrospectively in many cases unless all such detail is collected for every isolate at first collection. In addition, even when collecting such information it may not always be reliable especially when obtaining isolates second hand through diagnostic laboratories due to lack of time and/or reluctance of owners to supply all the relevant information especially when multiple treatments have been used.

CVMP comment

It is recognized that it would not be always possible to establish the clinical origin of the sample; this has now been taken into account in the text.

GENERAL COMMENTS - OVERVIEW

- It is unclear how the routinely collected data will be used by CVMP. This has to be more clearly explained and defined before mandated monitoring can be discussed. It is assumed that the request for post-approval monitoring exclusively refers to the target pathogens included in the SPC, not for off-label pathogens.

CVMP comment

The commitment will be tailored to the issues raised during the assessment.

- A clear definition of what constitutes resistance has to be provided and agreed (clinical breakpoints or epidemiological (wild-type) cut-off values (ECV), EUCAST vs. CLSI clinical breakpoints).

CVMP comment

The text has been modified to take into account the comments on resistance. The text now indicates: "*with resistance phenotypes not previously described"*. The focus is on distribution of MIC values. Any definition of resistance should be discussed and agreed on each case dependant on the amount of information available.

- It is generally not possible to molecularly determine the cause of elevated MICs in every strain with an elevated MIC, let alone those that might actually have unusual phenotypes and possible new resistance genes. The Reflection Paper asks sponsors to 'evaluate their capability to transfer the resistance.' Strains may transfer resistance *in vitro* but that may not relate to the true *in vivo* situation. All in all, these activities are best suited for a research institute or academic research program, and are outside the scope of expertise and capacity of the MAHs. The MAH should be expected to continue to rely on published data on the molecular mechanisms of resistance and not be asked to test each and every isolate to determine its molecular mechanism of resistance.

CVMP comment

The paragraph has been reworded for clarity and now indicates: "*If isolates with resistance phenotypes not previously described are detected, they should be characterised, if possible by studying the resistance mechanisms and by evaluating their capability to transfer the resistance."*

GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
Introduction	IFAH-Europe - The introduction suggests twice that monitoring of zoonotic and commensal organisms is sufficiently covered with respect to PMA. Why not to limit this Guideline to target pathogens in food and companion animals? This is our main responsibility. Industry is already doing a lot on zoonotics and commensals.	The CVMP in the reflection paper recognises the existence of the zoonosis monitoring program, however this reflection paper might apply for example to new molecules and for companion animals which are not covered by the zoonosis program.
7-10	IFAH-Europe CVMP acknowledges that a number of monitoring programs are in place; although most may focus on zoonotic pathogens, the CEESA, GERMVET and national programs such as MARAN and DANMAP are testing animal specific pathogens as well as zoonotic pathogens.	Agreed, for this reason might be sufficient to provide a summary of those programmes as indicated on the reflection paper.
13-17	IFAH-Europe CVMP refers to ongoing national surveillance programs, yet clearly states that these programs are not comprehensive, nor are they intended to conduct the sort of studies outlined in the Reflection paper. It is very odd that the national programs, with competent, unbiased researchers, are not given the additional resources needed to conduct the work proposed herein, but instead the MAH, with little to no expertise or facilities to do so, is being asked to generate the data. This is a key point that requires much “reflection” in terms of the economic impact for MAH, the quality and applicability of the data that might be generated, and the potential effect on discouraging the introduction of new antimicrobial products.	New molecules not yet introduced in the market would not be included in the monitoring programmes and the reference material might not even be available for official laboratories for monitoring of resistance. Furthermore, monitoring programmes are focussed towards a certain number of antimicrobials and microorganisms which might not include the intended molecule.
17	IFAH-Europe What is meant by the phrase "aspects not covered or intended to be covered by official monitoring programmes"?	See above.

[1] Where applicable

GUIDELINE SECTION TITLE		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
23	IFAH-Europe A 'defined list of antimicrobials' will presumably be agreed on a case-by-case basis. Will this be linked to the OIE veterinary or WHO human critically important antibiotics lists?	The phrase has been deleted as did not provide relevant information
24	IFAH-Europe Which bacterial species? Only those on the label we assume, for which clinical efficacy has been demonstrated.	Target pathogens are label pathogens but in case of specific concern commensal and zoonotic bacteria might also be considered.
27-28	IFAH-Europe Please note that a statistical power of 80 % might be difficult, because some pathogens are relatively rare. Which trends of resistance are requested? Does this mean that the MAH has to conduct annual surveys? The susceptibility at a given time point should be the most crucial aspect for the Agency.	CVMP recognises that this might be the case, is indicated that those are general recommendations. The text has been changed to clarify this.
27-43	IFAH-Europe The section comprises some mandatory suggestions (e.g., valid laboratory methods) and some vague suggestions, which might be rather difficult or costly to fulfil. Therefore, we would like to see in line 26 to replace "include" by "could include, if possible", or a similar wording elsewhere in the document.	Agreed.
Line: 32/33	Prof. Dik Mevius Currently the ISO-method (BS EN ISO 20776-1:2006) is globally accepted as the reference method for susceptibility testing of rapid growing aerobic bacteria and should be referred to in stead of EUCAST	Agreed
34-35	IFAH-Europe Assessment of the "potential of therapeutic failure" is outside the scope of a surveillance program. This is embedded within a risk assessment and cannot be justified within this document.	The text has been clarified, now reads: *"If resistant isolates are detected, when possible, the clinical origin of the sample should be determined to assess whether resistance resulted in therapeutic failure."*

[2] Where applicable

GUIDELINE SECTION TITLE		
Line no.[3] + paragraph no.	**Comment and Rationale**	**Outcome**
	-Reliable historical data are difficult to obtain for clinical samples, as we know from VetPath and GermVet, as has been recognised in previous CVMP guidelines.	
	IFAH-Europe This activity already being addressed within CVMP 644 as part of the initial submission dossier and subsequent monitoring data is available from a number of national monitoring programs, including CEESA. Indeed, most sponsors rely heavily on national monitoring program data to articulate their analysis.	Addressed somewhere else.
Line 36:	Prof. Dik Mevius 'unusual phenotypes' is very unclear. Probably any microbiologist in SAGAM would have his/her own opinion on that. I would suggest changing it to: 'any phenotypes that are not part of the wild-type distribution'	Text has been modified to make more understandable the concept.
Line 38:	Prof. Dik Mevius Will be possible to require that companies will immediately submit information on new resistance mechanisms to the CRL? They could be asked to do it. And what will the CRL do with that information.	The text has changed the text, the CVMP or relevant regulatory body should consider the need to forward the information to other relevant authorities or Agencies.
53-60	IFAH-Europe For the characteristics listed in 53-60, this represents a major disincentive to invest in new products	The importance to human health of Antimicrobial Resistance cannot be stressed sufficiently. Applicants have to demonstrate the safety of its intended new products. With new substances is difficult to foresee which would be the evolution of antimicrobial resistance. It should be noted that request of post-marketing data could simplify the authorisation process which could be an advantage for applicants.
75-83	IFAH-Europe In lines 75-83 whereby it is stated that a Community Reference Laboratory is in place and is additionally supported by National	Addressed somewhere else.

[3] Where applicable

GUIDELINE SECTION TITLE		
Line no.[4] + paragraph no.	**Comment and Rationale**	**Outcome**
	Reference Laboratories. If these institutions are already in place to support the needs of the proposed surveillance program, then it is unclear why marketing authorization holders (with no monitoring program expertise) are asked to do the job of these government laboratories.	

[4] Where applicable