The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Veterinary Use

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EMEA WORKSHOP ON THE REQUIREMENTS AND PROVISION OF ANALYTICAL METHODS FOR DRUG RESIDUE CONTROL IN ANIMAL PRODUCTS

24 – 25 January 2000, EMEA, London

Summary

The EMEA Workshop on the Requirements and Provision of Analytical Methods for Drug Residue Control in Animal Products, which was held in association with the Pan European Regulatory Forum (PERF) programme, was attended by experts from the Committee for Veterinary Medicinal Products (CVMP) and its Safety Working Party (SWP), representatives from the European Commission, National Reference Laboratories, Community Reference Laboratories and from Industry, as well as from other Interested Parties. Representatives of the Collaboration Agreement of Drug Regulatory Authorities in European Union Associated Countries (CADREAC), which include Central and Eastern European (non EU) Countries, also attended the meeting. The workshop was chaired by Dr. Ray Heitzman.

The workshop provided for the first time the opportunity for all parties involved in analytical method development and residues surveillance to meet and review together the procedure for provision of appropriate analytical methods for surveillance of MRLs, to discuss proposals for streamlining the development processes of such methods and to develop proposals for efficient procedures for the future.

The workshop focused on three key areas for which an analysis was undertaken and recommendations were made for future follow up and implementation. The main questions for discussion were:

1. How should analytical methods approved by the EMEA be made availability to the European laboratories involved in residue surveillance?
2. What would be the appropriate and efficient development process for an analytical method for use in residue surveillance?
3. Which performance criteria should an analytical method fulfil?

Following formal presentations in a morning plenary session in which the problems were identified and possible solutions discussed, the workshop continued in the afternoon with discussions of the specific issues identified in three smaller breakout groups each comprising experts from all the different parties represented.

In the final plenary session each chair presented a summary of the discussion in the breakout groups which were consolidated with a series of conclusions and recommendations as presented below.

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Conclusions and Recommendations

1. How should analytical methods approved by EMEA be made available to the European laboratories involved in residue surveillance?

It was agreed by all that the analytical methods provided by the applicants and approved by the Committee for Veterinary Medicinal Products (CVMP) should be available to both the National and Community Reference Laboratories (NRLs and CRLs) for use in regulatory residue surveillance. The availability of the methods to the reference laboratories should however be further facilitated.

The new procedure established in Council Regulation (EC) No 1308/99, the most recent amendment of Council Regulation (EEC) No 2377/90, in which the EMEA submits the methods to national competent authorities after publication of an MRL in the Official Journal was considered satisfactory. The appropriate national competent authorities will need to be nominated by the Member States. The proposal of the EMEA to submit at the same time the methods to the appropriate CRLs as well was welcomed.

The EMEA will establish an archive of the analytical methods approved by CVMP including those previously assessed, which would be made available to national competent authorities and Community Reference Laboratories in accordance with the provisions of Regulation 1308/99.

It was agreed that the methods should be clearly linked to the applicant, giving details of the contact point in the company. Such information would facilitate the work of the laboratories when adapting the methods to their needs. In case of changes of responsibilities, addresses etc., updates will be provided by Industry.

A central repository for all analytical methods including adaptations and updates carried out by the reference laboratories should be established at a point to be defined by the European Commission. The meeting discussed whether the CRLs might be the appropriate central point. The role of the EMEA in this information exchange system shall be confirmed.

The issue as to whether the analytical methods provided by applicants within their MRL application were confidential was extensively and diversely debated. Commission representatives (DG SANCO) and CRL representatives thought that the SPS agreement would necessitate that the analytical methods can be made available also to third countries and could therefore not be treated as confidential. However, it appears the current provisions of Council Directive 81/851/EEC and Regulation 2377/90 would consider the methods as proprietary intellectual information of applicants. This viewpoint was stressed by Industry, in particular as MRLs are set for substances rather than products not providing specific proprietary protection for products of the sponsor. While clarification on the legal situation on this point by the Commission is required, it was the EMEA's view that in the longer term the need for full transparency would require that the methods are made publicly available. The possibility of an amendment to the legislation providing better proprietary rights to sponsor companies would provide protection to companies.

2. What would be the appropriate and efficient development process for an analytical method for use in residue surveillance?

An appropriate analytical method for monitoring of residues for the substance concerned needs to be provided by the applicant when requesting the establishment of MRLs. Whether this could be the method used in the residue studies, or another method more suited to the practical means for surveillance purposes depends on the specific situation for each substance. Such methods must be validated in accordance to Volume VI (future Volume 8) of the rules governing medicinal products in the EU.

The development of screening methods or so-called multi-residue should be the responsibility of the reference laboratories. Both reference laboratories and Industry agreed that communication with the sponsor companies in this process is beneficial. Representatives of the CRLs and NRLs stressed that methods provided by the applicants would be a good starting point for the development of multi-residue methods.

It was also a common understanding that the provision of additional key information obtained during the development of the methods, such as e.g. solvents tested, choice of extraction procedure or reasoning for the development of a specific method, would be highly beneficial and would facilitate the work of the laboratories. Such information was described as part of the Critical Analytical Modules (CAMs).

Industry expressed willingness to provide free of charge standards of marker residues (parent substances, metabolites) required for a specific method and whenever possible standard reference material in reasonable quantities to the laboratories. Regarding reference material it was stressed by Industry that incurred tissues may often not be available due to limitations of their storage. It was proposed that the co-ordination and storage would be best placed in the Commission. The meeting recommended that for practical reasons the provision of standard material should be made to the CRLs, which should act as central distribution point for NRLs.

A better communication and co-operation between Industry and laboratories in the future found general support.

One suggestion by the Commission (DG SANCO) was to involve the CRLs in the evaluation the analytical method within the MRL assessment procedure, in order to assess especially the routine applicability of the method.

It was noted that the current legislation does not include any such provisions and the formal involvement would only be possible if Regulation 2377/90 was amended. As an alternative the involvement of experts of a reference laboratory as part of the CVMP Rapporteur's team for the evaluation of an MRL application was discussed. The workshop noted these suggestions, which will be brought to the attention of the CVMP for further consideration.

3. Which performance criteria should an analytical method fulfil?

Analytical methods to be provided by applicants in the context of an MRL procedure must be validated in accordance to Volume VI (future Volume 8) of the rules governing medicinal products in the EU. Surveillance methods developed by the reference laboratories on the basis of MRL methods for both screening and confirmation purposes will need to fulfil the validation criteria defined in Commission Decision 93/256/EC (under revision).

The general agreement was that the requirements of Volume VI and Commission Decision 93/256/EC are in general compatible. A harmonisation as far as possible and appropriate, including harmonisation of terminology should be sought. The workshop recommended that a review of both sets of criteria should be undertaken. It was however emphasised that not all performance criteria laid down in Commission Decision 93/256 and its draft revision would be applicable to a method submitted with an MRL application, e.g. inter-laboratory comparison, validation criteria for limit of detection It was particularly pointed out that Commission Decision 93/256 is as well focussed on methods applicable for the detection of forbidden and unauthorised substances. Commission representatives (DG SANCO) as well as representatives from CRLs and NRLs, while supporting such harmonisation, raised concern that such activity should not jeopardise the adoption of the revision of Commission Decision 93/256/EC envisaged for the near future. These recommendations will be reported to CVMP.

Discussion of specific issues

Specific criteria on accuracy and precision would be addressed within the harmonisation exercise.

The issue, whether full validation would be necessary for all target tissues was not concluded. One breakout group considered that validation for all target tissues would not be required, but that validation in one carcass tissue and in one offal tissue might be sufficient, while the other group, which had addressed this point, concluded validation for all target tissues important in respect to surveillance of imports from third countries.

In respect to the question, how the validation of the analytical methods for MRLs for skin and fat in natural proportions in pigs and chicken should be carried out, the majority expressed the view that the validation for the combined tissue "skin and fat in natural proportions" would be required, rather than separate validation for skin and fat taking account of their natural proportions in the species concerned.

LIST OF PARTICIPANTS

EMEA Workshop on the Requirements and Provision of Analytical Methods for Drug Residue Control in Animal Products and 2nd PERF Meeting

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