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Veterinary Medicines and Product Data Management

European Medicines Agency Workshop

Medicines for bees - What the Agency can do to increase availability

14 – 15 December 2009, European Medicines Agency, London

Introduction

The European Medicines Agency acknowledges that the problems of the bee keeping sector and the decline in the bee population all over Europe and the world are complex and diverse. One of the concerns raised by concerned parties and Member States over the years is the lack of adequate medicines to treat bee diseases.

The European Medicines Agency has been active since many years in supporting the availability of veterinary medicines to treat diseases in animals where authorized medicines were lacking, and initiated or promoted initiatives on EU level in this respect.

This workshop is intended to contribute to the availability of medicinal products for bees, which is one of the problems identified for the bee keeping sector.

The workshop will bring together experts from the bee keeping and honey production section, experts in bee diseases and treatment of bees, representatives from the regulatory authorities of Member States, the European Commission, the animal health industry and other interested parties and provide the opportunity to discuss possible approaches forward to identify most needed treatment options for bees. The aim of the workshop is to identify, if this is possible, a list of substances that are essential for the treatment of bee diseases in Europe.

The workshop will address among others the following issues:

- The regulatory basis
  - The regulator framework and requirements for the authorisation of veterinary medicines for bees
  - Establishment of MRLs in honey
  - Residues of veterinary medicinal products used in treatment of bees
- Other initiatives regarding bee health
- Overview of bee diseases and available treatment options, including medicines for bees
- Situation of bee diseases and approaches taken in different EU Member States
- The beekeeper's perspective on medicines for bees, considering bee health and honey quality
- The viewpoint from the animal health industry with case studies from manufacturers of veterinary medicinal products

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Format of discussions

Following presentations identifying problems and ideas for solutions from the viewpoint of the different parties involved during the afternoon of 14 December 2009, the workshop will continue in the morning of 15 December with discussions of the specific subjects identified in 2 or 3 smaller breakout groups comprising each experts from all parties.

It is foreseen that each of the 2/3 groups should discuss the same items, with a different focus, and that proposals would be prepared considering in particular 1. Needs and problems met by bee keepers, veterinarians and specialists in bee diseases, and 2. Practical and regulatory aspects considering feasibility of authorisation as well as production and marketing of the required veterinary medicines and prepare **conclusions and recommendations**.

Following the presentations of the reports and suggestions of each break-out group, the discussions would be consolidated in the plenary with the intention that the workshop would agree on an analysis of the problems and make recommendations in respect to the issues to be followed up and implemented in future activities and *fora*.

The main questions to be discussed are:

1. **Analysis of current situation**
    - Critical diseases in beekeeping sector
    - Options for treatments
    - Are the options for treatment sufficient?
    - If not, could possible reasons for lack of treatment options be identified?
2. **Proposals for possible solutions / actions**
    - What medicines are needed to treat bee diseases?
    - Can essential substances be proposed?
    - What can be done to support the development of veterinary medicinal products for the treatment of bee diseases?

The following document provides summary information on elements that will be addressed at the workshop with the intent to facilitate the discussions.

The document provides details and references regarding the requirements to establish MRL in honey and obtain a marketing authorisation for a veterinary medicinal product intended for the treatment of diseases in bees. Please note that this part is for information. It is not the intention of this workshop to discuss the application procedure, data requirements or assessment approach.

Background document

1. Legal/regulatory background

A veterinary medicinal product may only be placed on the market or used in the EU when a marketing authorisation has been issued**.**

The procedures and requirements are laid down in Directive 2001/82/EC, as amended, or Regulation (EC) No 727/2004, respectively. There are three different procedures to obtain a marketing authorisation for a medicinal product in the EU: the national procedure (when the product is intended to be marketed in one single country of the EU), the decentralised procedure or the mutual recognition procedure, (when the product is intended to be marketed in several countries of the EU) as well as the centralised procedure (the marketing authorisation will apply to all countries in the EU).[1]

Before any marketing authorisation for a veterinary medicinal product intended for a food producing species can be issued, all pharmacologically active substances contained in the product have to undergo a safety and residue evaluation under Regulation (EC) No 470/2009 (replaced Regulation (EEC) No 2377/90) and either maximum residue limits (MRLs) have been established or there is no need to establish MRLs for the substance in order to ensure consumer safety (previously included in Annex I, II, or III of Regulation 2377/90). These requirements apply to veterinary medicinal products intended for use in bees and the safety of residues must have been considered regarding honey.

The classification of the substances assessed with the view to establish maximum residue limits is established by Community law (Regulation) following a scientific opinion of the Committee for Medicinal Products for Veterinary Use (CVMP) of the Agency and are directly applicable in all countries of the European Union. This procedure for establishment of MRLs is independent of the marketing authorisation procedure.

1.1. MRLs established for honey and authorised medicines for bees

So far the following substances have been included in Annex I or II of Regulation 470/2009 specifically regarding honey:

- Amitraz (MRL)
- Coumafos (MRL)
- Flumethrin (no MRL necessary)
- Tau fluvalinate (no MRL necessary)
- Oxalic acid (no MRL necessary)

[1] National procedure - when the product is intended to be marketed in one single country of the EU. In this case the application is submitted to the competent authority of the concerned country who will carry out the evaluation and conclude on the marketing authorisation. This procedure is now used rarely, but most of the old products were authorised nationally.

Decentralised procedure/Mutual recognition procedure - when the product is intended to be marketed in several countries of the EU. The application is submitted to the competent authority of one country who will carry out the assessment. The assessment is then submitted to the other concerned competent authorities for agreement. The outcome of the assessment and the marketing authorisation (if granted) in the original country are then "recognised" by the other concerned countries. These procedures exist since 1995 (mutual recognition) and 2005 (decentralised).

Centralised procedure - the marketing authorisation will apply to all countries in the EU. Only innovative products i.e. new substances with new indications or with new innovative delivery methods or biotech products are eligible for the centralised route. The application is submitted to the EMA, which will carry out the evaluation. The scientific opinion following the evaluation of the application by the CVMP will be transmitted to the European Commission who will take the final decision on the granting of the marketing authorisation valid in all countries of the EU. This procedure exists since 1995.

Several veterinary medicinal products for the treatment of bee disease, mainly varroasis, are authorised in the EU containing the above substances, as well as some other substances in Annex II for all food producing species, such as formic acid, camphor, menthol, thymol, essential oils (e.g eucalyptus oil) (see Heads of European Medicines Agencies (HMA) website: http://www.hma.eu/uploads/media/76_Questionnaire_-_Bee_products_in_EU_-_EMA-CMDv-36668-2009.pdf)

1.2. Requirements to establish MRLs for honey

In order to obtain the establishment of an MRL[2] in honey for a new substance an MRL application has to be submitted to the European Medicines Agency. The procedure for the submission of an application for the establishment of MRLs is defined in Article 3 of Regulation (EC) No 470/2009 and further explained in Volume 8 of the Rules Governing Medicinal Products in the European Union – Maximum Residue Limits (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol8_en.htm), available on the website of the European Commission.

The MRL application needs to be accompanied by a dossier comprising safety and residue data. The safety data comprise data to study pharmacological and pharmacodynamic properties, a battery of toxicity studies, and where appropriate data to consider antimicrobial effects. The aim is to establish an appropriate acceptable daily intake (ADI) for the substance concerned.

The need and consideration of residue data for honey has been addressed in the CVMP Guideline on Safety and Residue data requirements for veterinary medicinal products intended for Minor Uses or Minor Species (MUMS) (http://www.ema.europa.eu/pdfs/vet/swp/6678105en.pdf).

Assessment of residues in honey is more complex than in mammalian or avian tissues. In honey matrix, there is no time dependent depletion/elimination of residues as a result of pharmacokinetics (as in mammalian/avian tissues). Residues, once present in honey, largely remain there. Apart from possible chemical decay of a substance in honey matrix over time, the main variable responsible for the level of residues at harvest time is the honey yield (dilution effect), which in large parts depends on the production site (geographical area) and weather conditions at flowering time. These variables are unpredictable and not directly related to a specifiable period of time. Therefore, the only feasible withdrawal period in honey is a “zero” withdrawal period, i.e. that there is no need to specify an interval between last treatment and harvest of honey. Residue studies covering a reasonable range of commercial treatment conditions are needed to support this “zero” withdrawal period. According to the new MRL regulation, if the metabolism and depletion of the substance cannot be assessed, the scientific risk assessment may take into account monitoring data or exposure data.

If MRLs have already been established for another species the establishment of an MRL for honey requires submission of an application for the extension of the existing MRLs to bees/honey. In such a case normally only a residue file is required, because the acceptable daily intake (ADI) is the same regardless of the uses (target species).

The new MRL regulation also provides for the establishment of an MRL for a substance following a request from the European Commission, a Member State or an Interested Party, which is included in an authorised medicinal product in the EU, for use in situations when that substance is used off-label under the exceptional circumstances for the treatment of diseases where no authorised veterinary

[2] The term “establishment of MRL” is used independent if an MRL value is established (old Annex I or III) or no MRL is considered necessary (old Annex II)

medicinal product is available (Article 11 of Directive 2001/82/EC), but for which no MRL application has been submitted for the foodstuff or species concerned (here honey).

1.3. Requirements for a marketing authorisation for a veterinary medicinal product for bees

In order to obtain a marketing authorisation for any veterinary medicinal product an application must be submitted to the competent authority concerned (competent authority in (a) Member State(s) or the European Medicines Agency). A marketing authorisation for a new product must be accompanied by a dossier that includes the particulars and documents set out in Directive 2001/82/EC, as amended, together with h results of studies that meet the technical requirements specified in Annex I to the Directive.

The following documentation is required to be included in the dossier:

- pharmaceutical (physico-chemical, biological or microbiological) tests,
- safety tests and residue tests,
- preclinical and clinical trials,
- tests assessing the potential risk posed by the veterinary medicinal product for the environment.

The safety and residues data will be largely identical to the data necessary for the safety of residues evaluation and establishment of MRLs.

Detailed guidance on the application and data requirements are provided in the Notice to Applicants - Volume 6 of the Rules Governing Medicinal Products in the European Union available at the website of the European Commission (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-6/a/vol6A_chap1_2007-01.pdf) and in CVMP guidelines regarding quality, safety and efficacy are published by the European Medicines Agency (http://www.ema.europa.eu/htms/vet/vetguidelines/background.htm).

Considering that bees are a so-called “minor species” certain reduction of data requirements will normally apply. Specific guidelines addressing adapted data requirements for Minor Uses and Minor Species (MUMS) have been prepared by the CVMP with the aim to facilitate authorisation of veterinary medicines for MUMS (http://www.ema.europa.eu/pdfs/vet/qwp/13367205en.pdf).

In addition, in order to provide incentives to companies to develop products for minor uses and species the Agency has put is place a series of measures ranging from administrative assistance, through fee reductions covering all aspects of applications (including scientific advice MRLs and marketing authorisation applications) for eligible products. Information on the policy and how to apply for such incentives are to be found at: http://www.ema.europa.eu/htms/vet/availability/availability.htm.

The proposals are intended to supplement of the measures already exist to assist applicants that are small to medium sized enterprises (SMEs) and that such companies are often interested in marketing products for limited markets such as bee products. For further information, see: http://www.ema.europa.eu/SME/SMEoverview.htm

1.4 Residues in honey

Monitoring of residues in honey is part of the national residue plan adopted and implemented by Member States according to Directive 96/23/EC. The minimum number of samples to be taken is 10 per 300 t of annual production plus 1 sample for each additional 300t. 5 345 targeted samples were taken by the EU Member States in 2008, out of them 93 were reported non-compliant, 88 of them for antibacterial substances and the rest for contaminants (pesticides and heavy metals).

Honey imported from third countries is also controlled in order to monitor residue levels in accordance with EU legislation.

2. Bee diseases - problems in bee keeping

The spread of bee diseases occurring in Europe varies to some extent between countries and regions. The most important bee diseases in Europe are currently:

- Varroasis (*Varroa destructor*)
- Nosemosis (*Nosema apis*)
- American foulbrood (*Paenibacillus larvae)*
- European foulbrood (*Melissococcus plutonius)*

Also the Colony collapse syndrome (CCD) is considered as a problem for the bee keeping sector in many EU countries.

New threats are expected from:

- *Nosema ceranae*
- *Tropilaelaps mite*
- Small hive beetle
- Kashmir bee virus

At present authorised veterinary medicines are in large part only available for the treatment of varroasis (see 1.2. above). However, the availability of medicines for varroa does not necessarily mean that no further medication option would be required.

For the treatment of other diseases hardly any authorised veterinary medicinal product is available.

Among scientists the views regarding the use of veterinary medicines in bees is not unambiguous. While it is recognised that antibiotics are used in some countries outside the EU in the prevention of bee diseases (in the EU no MRLs for antibiotics have been established for honey) their use is viewed controversially, due to concerns regarding residues and resistance development. Concerns regarding resistance could also occur with other types of substances, and beekeepers ideally would seek to have a choice of veterinary medicines available that would provide for sustainable treatment options.

3. Essential substances for the treatment of bees

The pharmaceutical legislation of the European Community pursues the twin objectives: the protection of human and animal health and of the environment and the free movement of veterinary medicinal products. Authorised veterinary medicines provide for efficacious and safe products available to the users, i.e. the bee keepers, and the environment, and ensure safety of consumers of honey and honey

products through the safety of residue evaluations and establishment of MRLs.. An authorisation of a medicine for bees will include the clear advice on the use of the product including also, if appropriate, any safety warnings, thus maximising efficiency, minimising resistance or other potential adverse effects.

It is recognised that veterinary medicinal products for the treatment of bees constitute products for a very limited market. Consequently turnover may not be sufficient to allow the investment required for product development and maintenance of a marketing authorisation and as result these product may not be of interest for many animal health companies.

If a small number of substances that are essential for the treatment of bee diseases could be identified, this could help to concentrate efforts on the compilation of the required data for the MRL and marketing authorisation applications.

4. References

Directive 2001/82/EC: Directive 2001/82/EC of the European Parliament and the Council of 6 November 2001. *Off. J. Eur. Comm.* L311: 28.11.2004, pp. 01–66, as amended by Directive 2004/28/EC of the European Parliament and the Council of the 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medical products. *Off. J. Eur. Comm.* L136: 30.04.2004, 58–84. Available at:

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Regulation (EC) No 727/2004: Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. *Off. J. Eur. Comm.* L136: 30.4.2004, 1–33. Available at:

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726_cons/reg_2004_726_cons_en.pdf

Regulation (EC) No 470/2009: Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council, *Off. J. Eur. Comm.* L152: 16.6.2009, 11-21. Available at:

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-5/reg_2009-470/reg_470_2009_en.pdf

Volume 8 of the Rules governing medicinal products in the European Union – Maximum Residue Limits: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol8_en.htm

Volume 6 of the Rules governing medicinal products in the European Union: Notice to Applicants and regulatory guidelines for medicinal products for veterinary use: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol6_en.htm

Directive 96/23/EC: Council Directive 96/23/EC of 29 April 1996 on measures to monitor certain substances and residues thereof in live animals and animal products and repealing Directives 85/358/EEC and 86/469/EEC and Decisions 89/187/EEC and 91/664/EEC, *Off. J. Eur. Comm.* L125, 23.5.1996, 10-32. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31996L0023:EN:HTML