EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 March 2010
EMA/28057/2010

Workshop on medicines for bees - What the Agency can do to increase availability

14 - 15 December 2009, London

Report

Executive Summary

The European Medicines Agency, on 14-15 December 2009, held a workshop to discuss a specific aspect concerning bee health – the availability of medicines for bees in Europe, in particular what medicines are needed and what the Agency can do to increase the availability of needed medicines.

It is acknowledged 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 interested 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 authorised medicines are lacking, and initiated or promoted initiatives on EU level in this respect. Therefore, the Agency organised this workshop aimed to contribute to the availability of appropriate treatment options for bees.

The workshop brought 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. The aim was to provide the opportunity to discuss possible approaches forward and to identify most needed treatment options for bees, including consideration of practical aspects of how to achieve marketing authorisations for bee medicines.

Following presentations providing comprehensive information of the existing activities in Europe concerning bee health, identifying the problems that the bee keeping community and veterinarians are facing, and proposing ideas for solutions from the viewpoint of the different concerned parties, the meeting split up in two breakout groups to discuss specific points identified in the plenary session as key elements towards providing adequate medicines for the treatment of bees.

One group concentrated on providing an analysis of the current situation, by identifying the critical diseases in the beekeeping sector, discussing the options for treatment, and whether the available options for treatment are sufficient, and identifying possible reasons for any lack of treatment options. The second group's task was to consider issues of feasibility and prepare proposals for actions that could support the availability and use of authorised veterinary medicinal products for bees. The proposals should address availability of existing authorised veterinary medicines as well as development of new medicines.

Following the presentations of the reports and conclusions of each break-out group, the discussions were consolidated in the plenary.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8447
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

© European Medicines Agency, 2010. Reproduction is authorised provided the source is acknowledged.

The overall conclusions and recommendations of the workshop were:

- The problem of bee health and appropriate treatment of bees is much more complex and diverse than simply identifying some potentially needed medicines.
- An overall strategy regarding medicines for bees should be established. Such a strategy should identify for each bee disease whether medication was appropriate, and if medication is the choice of treatment, which medication should be applied as well as the conditions for the appropriate action or treatment be clarified.
- The information available to beekeepers on good beekeeping practice should be improved. Adequate information or training of beekeepers would ensure correct use of medicines. This was seen as a role of governments.
- It should also be explored if specialised training on bee diseases could be provided to veterinarians. *[Post meeting information: DG SANCO is funding a training programme on bee diseases for official EU vets under its Better Training for Safer Food initiative, which will start in 2009]*
- The use of only authorised veterinary medicines in beekeeping should be pursued as goal. Chemical substances currently used for the treatment of bee diseases should be authorised as veterinary medicines to ensure that they are adequately formulated for the intended use and correctly applied.
- The proposal was discussed whether certain veterinary medicinal products for bees could be exempted from prescription to facilitate access by the bee keepers.
- Better use should be made of existing marketing authorisations for bee medicines so that the authorised veterinary medicines would be available in all countries across the EU and existing legal provisions should be explored to achieve this. For the future revision of the veterinary legislation further facilitation of the authorisation of veterinary medicines for bees should be considered.
- Further research is needed for the development of new/alternative treatment options and to identify essential substances. An expert group should be created to prepare a proposal for a treatment strategy.
- Substances with existing marketing authorisations for other species and existing MRLs or substances not requiring an MRL (former Annex II substances) are considered more likely for achieving a marketing authorisation than an entirely new molecule or substances without MRL.
- Approaches like the example of oxalic acid, where several parties worked in cooperation, should serve as model for future attempts to achieve a marketing authorisation for a veterinary medicinal product for bees.
- The veterinary pharmaceutical industry shows interest in developing medicines for bees. However the industry also faces obstacles that hinder development and marketing of medicinal products for bees. In order to develop new medicines for bees incentives, in particular adequate data protection, would be needed.
- The meeting considered that continued discussions were necessary to find solutions. It was recognised that many of these aspects of the debate were outside the scope and mandate of the European Medicines Agency, and the further discussions would possibly need to involve additional partners. The efforts by the Agency to organise the meeting and allow these discussions were appreciated and further activities welcome.

Report of the meeting

Presentations:

1. Medicines for bees

- Introduction to subject and aim of workshop

I. Koudouna (EMA) introduced the subject, summarising the potential reasons for the decline on bee populations discussed by experts and listing the main bee diseases in Europe. One concern that was repeatedly mentioned over the last years by interested parties and member states was the lack of adequate veterinary medicines to treat bee diseases. Not only the lack of medicines may hinder treatment but the use of unauthorised products or the use of chemical substances as raw materials give also rise to concerns in respect to potential incorrect use of products/chemical substances, the absence of knowledge on their efficacy, the potential for undesired or illegal residues in honey, the safety of the bee keeper in applying the product and the potential environmental impact. She explained the role of the Agency to improve the availability of veterinary medicines in general and the aim of the workshop, i.e. to contribute to the availability of medicines for bees and to identify any essential substances for the treatment of bees, for which ultimately veterinary medicines could be made available.

- Role of the European Medicines Agency, Establishment of MRLs and authorisation of veterinary medicines in the EU

I. Duarte (EMA) outlined the Agency's role and responsibilities and gave an overview of the authorisation process of medicines for animals, in particular for food producing animals, which require the setting of a maximum residue limit (MRL) for the food commodity/species concerned before a marketing authorisation can be granted. Bees are classified as food producing animals in the EU thus the establishment of an MRL for honey is necessary before a marketing authorisation for a veterinary medicinal product can be granted. I Duarte provided particulars in regard to MRLs and medicines for bees, listing the substances for which MRLs have been established in the EU for honey and summarising the data required for applications for setting an MRL for honey bees and for a marketing authorisation for a veterinary medicinal product.

During the discussion it was questioned why the CVMP had indicated that in principle only medicinal products requiring a "0 day" withdrawal period should be authorised for bees. It was explained that in view of the lack of metabolism in the beehive an elimination of residues over a certain period of time as defined for other food producing species would not occur. It was however stressed that a decision was always taken on a case by case basis considering the data available to assess the residues resulting from the use of the product in practice.

2. European Initiatives

- Bee Surveillance Programmes and Bee Mortality in Europe

Dr. J. Richardson (European Food Safety Authority (EFSA)) gave an overview of the tasks of the EFSA and their activities regarding bee health. One ongoing activity concerns risk assessment guidance on ecotoxicology and environmental risk assessment and will include a tiered risk assessment approach for bees. Another activity, which goes back to the initiative by the French AFFSSA, concerned the bee surveillance programmes and monitoring of the bee mortality in Europe. The survey conducted in 2008 confirmed a general weakness of national surveillance systems. Although in 2003 and 2008 some countries indicated consistently higher bee losses than in other years, there were insufficient data to analyse a trend. Harmonisation of surveillance systems across Europe was needed. Literature research also indicated the multifactorial origin of colony losses and insufficient knowledge of the underlying factors for this. EFSA concluded therefore the need for more harmonisation of the European surveillance systems and its parameters/methodology.

In the following discussions Dr Richardson encouraged participants to send any comments they would have on the report or any findings to EFSA for consideration for future surveys.

- **Recent actions by the European Commission concerning bee health**

Dr. E. Soto (European Commission, DG Health and Consumers) gave an overview of the intra- and intercommunity trade with bees and bee products and explained the legislation for live bee imports. Import of live bees is restricted to queen bees and a restricted number of attendants. In addition, specific requirements regarding the health certification and packaging materials have to be respected. Legislation with regard to the import of certain live animals, including bees, is currently revised to be simplified into one single Regulation rather than having several legal documents, as it is at present.

Dr Soto also reported of an inter-departmental co-ordination group that has been set up within the European Commission aimed to improve cooperation and communication within the different Directorates General. Future policies within the Commission would include regular scientific expert meetings to discuss emerging threats and topical issues and the drafting of safeguard measures for Member States for bee diseases not yet observed in the EU. The inter-service group is also proposing to set up a pilot study for a more harmonised surveillance in Member States.

3. Overview of bee diseases and available treatment options

Dr. V. Jenčič (Veterinary Faculty, University of Ljubljana, Slovenia) gave an introduction into the structure and life of a honeybee colony, explained the criteria for the health of a bee colony, the defence mechanisms of bees and the colony and the reasons of the breaking up of the defence mechanisms. The diseases and pests in honey bees can be divided in infectious diseases (viral, bacterial, fungal and parasitical), pests and non infectious diseases. Diseases of a honey bee colony are brood diseases, adult bee diseases, pest and colony collapse disorder. She mentioned that the OIE Terrestrial Animal Health Code lists a number of bee diseases and hygiene and disease security measures are given. As main diseases and available treatment options Dr Jenčič identified:

- Brood diseases: The main brood diseases are American foul brood and European foul brood. The American foul brood is a disease requiring notification. No treatment options were available for the American foul brood and treatment with antibiotics is not allowed, as they do not kill the highly resistant spores. For American foul brood the destruction of infected colonies is compulsory. Also for the European Foul Brood there were no real treatment options. In some countries the use of antibiotics was permitted under certain circumstances, i.e. under veterinary supervision and applying long withdrawal periods. Therefore, usually the infected colonies were destroyed.

  Other brood diseases are Chalkbrood, Stonebrood and Sacbrood. No specific medical treatment is available for these. For Chalkbrood good beekeeping hygiene was the best prevention measure. For Stonebrood, which is a zoonosis, urgent destruction of infected colonies and honey was compulsory. For Sacbrood hygiene measures and replacement of the infected queen were recommended.

- Adult bee diseases: There are several viral diseases, for none of them a specific medical treatment is available and hygiene measures were the method of prevention. Nosemosis (*Nosema cerana*, *Nosema apis*) is a parasitic disease in adult bees, for which fumagillin is highly effective for treatment. However, as no MRL could be established due to the inadequacy of data available to ensure consumer safety, the use of the substances is not allowed. Prevention procedures need to be applied.

- Varroasis: Varroasis is caused by the mite Varroa destructor. Several treatment options available – biotechnical methods like drone brood removal, comb trapping and use of chemical substances, however none was perfect. The best results were achieved with a combined treatment ("integrated varroa control") and also if all beekeepers in a region were to treat bees at same time with same method to keep resistance low. The chemicals/veterinary medicines are applied by different routes of administration (spray, smoke, contact). Not all chemical substances that are/could be used have MRLs/ are authorised as medicines.

- Other bee diseases, which are however not (yet) in Europe, are infestation with mites from Tropilelaps, Acarapis wood as well as small hive beetle. For the latter the treatment was similar to varroa.

- Colony Collapse Disorder (CCD) is observed worldwide. It is a multifactorial disease resulting in disappearance of bees. No treatment strategies are yet available.

Dr Jenčič concluded that a different beekeeping strategy was needed with more research in honeybee biology and physiology and research in bee medicines, such as alternative treatments (e.g. pheromones).

4. Medicines for bees: current situation and future aspects

Dr. W. Ritter (OIE Reference Laboratory at CVUA, Freiburg (Germany)) outlined the problems with medicines for bees, the current situation and future aspects. The current perception of many beekeepers would be that any treatment that helps to fight diseases is allowed. However, the safety profile of the medicines, ensuring safety of the user, consumer safety, effectiveness and low side affects to the bees should be the choice.

He pointed out that treatment might result in residues of hydrophilic substances in honey, while lipophilic substances would accumulate in the wax, which due to the process of wax recycling and comb foundation could eventually lead to contamination of the honey.

He reviewed the different application routes (feeding, trickling, strips, vaporization and evaporation, spraying and dusting) and the pros and cons in respect to their risk for the applicant, their risk for food contamination and their extent of efficacy or tolerance in the bee or their brood.

The specific situations regarding certain bee diseases were analysed.

Nosemosis presents a problem, in particular in southern Europe. No authorised medicines were available and other control measures were applied as well as anti-coccidial medicines under off-label use. These anti-coccidia, which seem to be effective, should be further explored as future bee medicines.

For the American and European Foulbrood no authorised medicines are available, some antibiotics show efficacy against the bacteria in the larvae, however not against the spores, these can only be destroyed by eradication (e.g. burning).

Varroa infestation remains the currently most important disease in bees, not only with regard to causing varrosis but also by introducing viral diseases. While several veterinary medicines were authorised, there is concern for the future due to observed resistance against synthetic anti infectious medicines, and the uncertainty of effectiveness of natural anti infectious substances. Potential future treatment options include genetic therapy or prophylactic vaccination.

Dr Ritter recommended that authorisation of bee medicines should be made easier and better harmonised across Europe and innovative developments should be encouraged.

In the discussion following this presentation the need for facilitation of authorisations for bee medicines across Europe was supported, proposals were made for automatic approval of medicines, meaning that a medicine authorised for bees in one EU country would be automatically authorised in other EU countries and simplification of distribution of bee medicines across Europe was recommended.

5. Veterinarians and Bee health involvement, taking France as an example

Dr N. Vidal-Naquet Federation of Veterinarians of Europe (FVE) presented proposals regarding the involvement of veterinarians in bee keeping based on the approach taken in France and reflections on further actions. While beekeeping is no longer part of the routine curriculum at the French Veterinary education, a high standard diploma course has been set up in 2005 on beekeeping and bee keeping pathology. The three week course enables veterinarians to understand the principles of beekeeping but also the pathology and management of various conditions. These specialised veterinarians are/will be able to work with the beekeepers in managing of the diseases as well as be involved in research and diagnostics development.

The non-availability of effective veterinary medicines for bees causes challenges for beekeepers, veterinarians as well as for regulatory authorities and pharmaceutical industry. The problems encountered were analysed in detail at the example of the treatment of Varroa destructor. A number of veterinary medicines are authorised in France, with one product allowed as prescription only. The problems experienced by beekeepers which may lead to not achieving fully successful treatment can have different causes, e.g. resistance development, lack of efficacy and non-optimised practices in the treatment regimen. Further clarification through scientific studies would need to be achieved on some key questions in order to identify if veterinary medicines are needed to treat the diseases, and if confirmed, which essential medicines are lacking.

Experience from the United States would have shown that widespread use of some of these substances resulted in increased resistance. A better availability and clearer / easier authorisation of veterinary medicines for bees and consistency across the EU was encouraged. It would need to be reviewed and clarified which veterinary medicines are necessary, and then efforts made to establish MRLs in honey and obtain marketing authorisations. In particular the use of antibiotics and anti-coccidial medicines should be clearly regulated in order to limit resistance. The veterinarians would have the responsibility to define the need for veterinary medicines in honey bee diseases.

In the discussion following the presentation the meeting was informed that in the former Middle and Eastern European countries veterinarians were usually involved in treatment of bee diseases, in particular advising beekeepers on best treatment options. The European Commission has recently introduced training courses for veterinarians. From the beekeepers side it was pointed out that involvement of veterinarians or veterinary services should be free of charge, otherwise beekeepers would not use such service.

6. The situation in Member States

An overview of the bee health situation in EU Member States was given at the examples of the United Kingdom, France and Greece.

Mr Selwyn Wilkins, on behalf of Mr Mike Brown, (National Bee Unit (NBU) of the Food and Environment Research Agency (fera)) and Dr M. Spagnuolo-Weaver (Veterinary Medicines Directorate (VMD)) presented the situation in the UK. The developments of bee health and losses in the UK over the last decades were presented based on NBU data. A steady increase of colony losses is being observed since 2001, for which the causes are assumed to be of multiple nature. Research projects to better understand the causes for the colony losses have been initiated and first results are being reviewed.

With regard to the availability of veterinary medicines for bees the UK has set up an action plan with short, medium and long-term objectives including fee incentives for licensing of bee products, research work in residue and efficacy issues for substances needed for bee disease and proposals for changes in the legislation e.g. prescription of bee products by qualified professionals (not necessarily veterinarians). It was clarified that the use of oxytetracycline is allowed in the UK under the cascade for the treatment of the European Foulbrood with the withdrawal period of at least 6 months.

Dr Marie-Pierre Chauzat (French Food Safety Agency (AFSSA)) summarised the situation for France. In France, use of some authorised bee medicines indicates that efficacy appears to be decreasing, and e.g. due to observed resistance development, fluvalinate would no longer be recommended for varrosis treatment. Beekeepers were asking urgently for medicines against varroa, nosema and foulbroods. In absence of effective medicines, beekeepers would use alternative "homemade" treatments to treat disease, in particular for varrosis, with unclear and inconsistent conditions of use. According to recent studies it was concluded that colony winter mortalities are largely due to Varroa deleterious effect caused by inappropriate treatments. Dr Chauzat considered that in light of resistance developments, uncertain efficacy of existing treatment options and frequent use of home made treatments there would be an urgent need for the development of new treatments against varrosis.

In France, the treatment of American foulbrood is acceptable provided that the disease is not yet largely developed. Honey and wax would be destroyed.

Dr A. Tsigouri (National Organization for Medicines (EOF)) gave a summary of the situation in Greece. She presented statistical data on the Greek apiculture and surveillance results on be diseases. The

most prevalent disease is Nosemosis (over 40% of samples positive to some pest or disease were *Nosema* positive) followed by Varroosis, European Foulbrood and American foulbrood, as well as other bee diseases (mostly brood diseases). For nosemosis treatment with fumagillin had been used for the years 2000-2005 under the direct supervision of the State Veterinary Service with specific prescription for one treatment only and long time away from honey collection. However, after a recommendation made by DG SANCO following an inspection visit of FVO in April 2005, to stop using an active substance not listed in Annex I-III of Reg. 2377/90, this procedure had been terminated. For varroosis seven products (4 active substances) are authorised. She called for more consistency between Member States in authorisation and control of use of medicines in bees. She pointed out that "cascade" provisions for off-label use would not be helpful in the case of bees, when no MRLs have been established in honey resulting in "zero" tolerance. In addition, she noted that while marketing authorisations are needed for all veterinary medicines containing the substances allowed for organic beekeeping, this is not clear to all beekeepers. She concluded that Greek beekeepers require urgently more medicines for bees and consistent attitude through Europe.

7. The beekeeper's perspective

- **Securing bee health and honey quality**

Introducing his presentation E. Bruneau (COPA-COGECA) pointed out important specificities of bees that have an impact on bee health and on honey quality: The differences between bees and other livestock animals, the specificities of beekeeping in relation to other livestock sectors, veterinary specificities of beekeeping, which would need to be addressed in the EU animal health policy and that honey, pollen and royal jelly would not be common food products. He explained the uniqueness of the bee with the colony being a "super-organism" with the health status of the colony depending on behavioural integrity of the individuals who compose it.

He reviewed the situation regarding varroa, which he considered an emergency situation as highest cause for mortality and a problem of availability of medicines. While several veterinary medicinal products are authorised in the EU, they were not available in all countries, in addition some were difficult to obtain for beekeepers as they are prescription only and for half of the active substance the varroa mite has developed resistance. He called for extension of existing authorisations of anti-varroa medicines to all Member States, more flexibility in the conditions for use of medicines under the "cascade", the recognition of the phenomenon of a large-scale resistance, and the recognition of the importance of two treatments with different active substances and obligation of alternation of active ingredients over the years. The development of new active substances – miticides – should be encouraged.

In respect to bacterial diseases - in particular the American foul brood - he considered the use of antibiotics inappropriate as they would only camouflage the disease. So far there would be no common strategy in Europe with some countries using antibiotics other require destruction of colonies. He proposed a control strategy, with destruction of bee hives only when clinical signs, and supported possibly genetic selection.

Regarding the control of opportunistic diseases he pointed out that bees are able to naturally defend themselves except in cases of disturbances. Therefore, improving the disease control should not only deal with the treatment of disease but focus on disease prevention and improve the bee environment. The risk of residues in honey should be minimized in view of the high number of honey imported from third countries. In respect to the role of medicines he called for measures to control residues in bee products and for the adaptation of the EU health policy to beekeeping needs. The procedures for medicines should be specific for bees/bee products focusing on disease prevention and aiming to minimise the risk of residues, favouring "natural" substances. In order to improve disease control, beekeepers and veterinarians should be trained. Also specialized centres for bee pathology and research regarding the emergence of opportunistic diseases and improvement of the bee environment (plant diversity) should be aimed for.

In reviewing the difference in the production of honey in the EU vs third countries, he pointed out that honey has in the EU the image of a "natural" and "healthy" product. Antibiotics were being used in

beekeeping of third countries but were not authorised in the EU. There was also the possibility of contamination through the environment. He pointed out that 1/3 of the sanitary alerts due to "residues of veterinary medicine" in food were residue contaminations of honey and royal jelly. He called for establishing a level for the control of residues to assure trade and consumer protection; such level should be sufficiently low to maintain and protect the quality and positive image of bee products; such levels could be either reference points for action or an MRL, to be investigated, under the new MRL regulation.

- The beekeeper's perspective on medicines for bees

W. Haefeker (European Professional Beekeepers Association (EPBA)) presented the beekeepers perspective on medicines for bees. He pointed out that pathogens would always be present in bee colonies and that the ability of bees to handle natural pathogens load would depend on the diversity of food sources and that despite the hives being infected, bees in a healthy environment were usually without clinical symptoms.

He compared the different types of honey on the market pointing out that honey in the EU would be mostly regional products, not highly processed, largely residue free and often organic produced. Beekeepers would provide free pollination, different to the situation in the USA where pollination is the main revenue source for beekeepers and honey would be the by-product.

He considered that availability of medicines as such would not solve problems with regard to bee health as seen when comparing the EU situation with the USA, where a wide range of medicines including antibiotics were easily available to the beekeeper over the counter or via mail order. However, the USA suffers among the highest rate of colony losses in the world. With regard to Foul Brood, antibiotics mask the problem and other methods such as shook swarm method and moving treated hives into an area with good nectar flow appear good options. Also promoting breeding programmes, e.g. with disease resistant queens, might be an option. Experience from New Zealand where treatment options were changed should be noted. Concerning varroa treatment, optimisation of available treatment options are recommended, e.g. by using stripos that could be used in hives of different sizes. Development of non-chemical methods might also be future treatment options e.g. using varroa antagonists (virus) or molecular vaccines. Presence of pesticides might show more impact on bee health than previously anticipated.

He concluded that the health of honey bees is reflective of the surrounding environment and that medicines were no substitute for making sure the environment does not become hostile to bees nor were they a substitute for good beekeeping practices. Beekeeping methods need to take advantage of natural defenses and genetic resources within bee populations. There is much room for improvement in application of organic acids to combat varroa, and much room for improvement in the strategy to fight the American Foulbrood. Additional medicines may be welcome as a last resort but the residue contamination of bee products was a very important consideration. Many beekeepers especially the rising number of organic beekeepers would not use products that may compromise the wholesale image of their bee products.

8. The perspective of the honey trading industry

F. Filodda (*European Federation of Honey Packers and Distributors (FEEDM))* described the situation of the honey trade and addressed the problem of antibiotic residues in honey, which were frequently found in honey imported from third countries due to the use of antibiotics. He remarked that the use of antibiotics was however not restricted to third countries, but they would also be used by beekeepers in the EU.

Antibiotics would particularly be used in case of Foulbrood infestations, as beekeepers would fear the loss of their beehives. The main antibiotics used were streptomycin, sulfonamides, tetra-and oxytetracycline, tylosin and macrolides. Some of the antibiotics would be authorised in third countries and their use legal. In the EU the use of antibiotics was not allowed and no MRLs have been established. The resulting "zero tolerance" policy of residues would cause significant trade problems as

clear, harmonised rules did not exist with regard to acceptable control methods, detection limits or sampling methods, resulting in different interpretation by EU Member States. Applications for the establishment of MRLs and marketing authorisations for veterinary medicines in bees would be difficult due to several reasons: to establish MRLs in honey is often difficult due to the particular residue situation which results in residues remaining in the bee hive after treatment. This also leads to the effect that withdrawal periods cannot be established in a similar way as for other tissues. The concerns that the use of antibiotics may not be helpful were shared, and other options could be considered, also aimed to maintain the image that the public has of honey. However, he called for regulatory actions to overcome the current situation, and recalled the example of oxytetracycline, where an MRL was not established despite the fact that an MRL application was submitted and a recommendation was made by the CVMP. He also criticised the lack of action and consistency of regulators illustrated at the example of a recent correspondence of FEEDM, with the Commission and the EMA, where MRLs had been requested for several antibiotics and inconsistent responses had been received.

In the subsequent discussion the chair clarified, that the response letters from the Commission and EMA had been in fact consistent. The request to the EMA had been to establish reference points for actions (RPA) in order to allow for control of honey imported from third countries. In this respect the response of EMA was to clarify that they are not responsible for RPAs and therefore such a request would need to be addressed to the European Commission. In what concerns requests for the establishment of MRLs for substances used in third countries, such requests could only be submitted to the EMA by Member States or the Commission. On the other hand, the Commission, in their response had considered that RPAs were not appropriate for the case in question, but a request to the EMA for the establishment of MRLs under specific conditions of Art 9 of the new MRL Regulation should be explored. The Commission representative considered that with the newly set up co-ordination group any co-ordination issues regarding activities in the bee health field should be overcome. It was explained that educational measures might be helpful for the honey suppliers; it was also pointed out that such programmes were already set up in many countries. In respect to the levels for RPAs proposed by FEEDM, it was pointed out that these levels were very ambitious to achieve in any screening method, in particular for fluoroquinolones, as the matrix, honey, posed challenges for analytical methods.

9. The perspective of the animal health industry

- Why is the availability of VMP for bees so narrow? What could be done to increase this availability?

Dr Bill Vandaele representing the Association of Veterinary Consultants (AVC), highlighted the specificities of bees and their treatments and pointed out the environmental benefits of bees and their importance for pollination. He recalled that the issue of inadequate availability of medicines for bees has been addressed in general at many occasions before in discussion *fora* and very recently at the worldwide beekeepers APIMONDIA congress. He reviewed the situation in some EU countries, using the example of Belgium to highlight the difficulties beekeepers face. He considered that in Europe the vast majority of bee treatments with chemical substances are not in line with legislation due to the lack of authorised medicines, and often pesticides or bulk chemicals were used. For some substances the first step towards a veterinary medicine has been done and MRLs were established (or classification "no MRL necessary") but no veterinary medicines were authorised or on the market.

He considered that in order to find solutions it would be necessary for all parties concerned to work together. Multiple elements need to be considered to be successful and he reminded of the FVE guidelines on Good Veterinary Practice, e.g. regarding varroasis. He supported recent EMA proposals such as the development of a guideline regarding veterinary medicines controlling parasitosis in bees and called for consideration of the environmental impact regarding pollination in the cost-benefit considerations for medicines. He considered the impact of MUMS requirements in the development of a veterinary medicine for a minor species too insignificant to provide an incentive for developing a product for bees. Therefore, the responsibilities and costs should be shared, between EU and national regulators, academic and research institutes and industry. Lessons could b learned from the USA MUMS system. He reminded that the possibilities for obtaining funding in the context of the ETPGAH or specific EU legislation regarding bees should be explored.

- Animal Health Company Experience: Case studies from manufacturers of veterinary medicinal products

Dr Erik de Ridder and Mr Guillaume Agede representing the International Federation for Animal Health Europe (IFAH-Europe) recognised the concerns regarding bee health and honey quality. They acknowledged that beekeepers were confronted with many challenges due to diseases and that the lack of therapeutic options was a major concern. The R&D based animal health companies share the concern from the society as a whole and see the value for the beekeepers. However, the speakers pointed out that the animal health companies were confronted with several issues that hinder bringing medicines for bees to the market: the market is relatively small, the need for MRLs without any data protection and most of the suitable medicines were old and therefore equally not eligible for data protection. These difficulties were illustrated with three case studies involving oxalic acid, fumagillin and tylosin.

Oxalic acid: Following activities by a consortium to put together an MRL application, an MRL classification was successfully achieved in 2003. Industry worked with the competent authorities in Spain to define a veterinary medicinal product for bees and a marketing authorisation was issued in Spain in 2007 and the product launched. The sales however were low. Several Member States requested that an MRP was launched, but as a first step it was proposed to use the cascade system. No use of it really occurred. An import permission granted by one Member State did also not result in sales. Beekeepers would continue to use oxalic acid as unauthorised raw material as it is easily accessible and less expensive. This example would illustrate that even good collaboration between industry and authorities no return on investment for industry may result and at the end companies would not keep the product on the market.

Fumagillin: Fumagillin was on the EU market since 1970 for the prevention and treatment of nosema disease in bees. In addition later a veterinary medicinal product containing fumagillin for trout was developed. However, as MRLs could not be recommended by the CVMP, no marketing authorisation could be maintained or issued for bees. The CVMP acknowledged that fumagillin would be an essential substance for veterinary medicine for bees (EMEA/CVMP/411/00). Since then and in a new regulatory context considering MUMS data requirements to establish MRLs and having obtained free scientific advice for MUMS, new work on toxicity studies is ongoing.

Tylosin: Tylosin has been used in bee-keeping globally and has received approval in the USA from FDA based on a dossier in which USDA and industry have worked together. The registered claim is for the treatment of American foulbrood in honeybees. Efficacy, safety and residue studies were available. In the EU, MRLs have been set for all food producing species, however, no MRL for honey has been set so far. The UK beekeepers association has requested the originator to apply for a marketing authorisation and the company was initially receptive to the idea. However, Dr de Ridder expressed concerns over what questions might still arise within the evaluation of the MRL dossier that might lead to further data requirements, even for the minor species and the minor use, as they have experienced in a similar case previously. Furthermore, the 'global marketing authorisation' concept, as created by Article 5 of Directive 2004/28, would prevent data protection for the dossier: therefore any work done by the company would immediately be available for the generic competition. The lack of data protection, preventing return on investment, was considered the biggest hurdle.

In summarising the speakers recognised the interest for society and value for beekeepers for medicines for bees but pointed out that the lack of data protection and the small market size are obstacles for developing products. However, industry still sees hope if the needs of honeybees and their keepers would be seen as critical for agriculture and society, benefit-risk analysis would allow product development studies to progress and adequate data protection could be provided.

10. Breakout sessions

Following the presentations and discussions two break-out groups were formed, which discussed the matter in parallel sessions and prepared proposals and recommendations for possible solutions / actions. Subsequently the two groups reported back to the plenary and their considerations and conclusions were reviewed. The considerations and conclusions, as overall outcome at the plenary meeting, are summarised below.

Group 1: chair: Mr E. Bruneau (COPA COGECA), rapporteur I Duarte (EMA)

The group's task was to provide an analysis of current situation, identify the critical diseases in the beekeeping sector, the available options for treatment and conclude whether the options for treatment available are sufficient. If insufficient, possible reasons for lack of treatment options should be identified.

In a second step proposals for possible solutions and actions should be developed, and where possible the medicines that are needed to treat bee diseases be identified and proposals for essential substances made.

- Analysis of current situation

a) Critical diseases in the beekeeping sector

As critical diseases the following were identified:

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

New threats are expected from:

- *Tropilaelaps mite*
- Small hive beetle

b) Available options for treatment

c) Are the options for treatment sufficient?

<u>Varroa</u>

- Treatment is available although there are problems of resistance and of efficacy
- Strategy for control and treatment is needed – New ways of treatment and new medicines are needed
- Medicines are available but not equally at European level

<u>Nosemosis (Nosema apis and Nosema ceranae)</u>

- Prophylaxis is essential
- Good beekeeping is the key
- Options for treatment are needed – Antibiotics and coccidiostats are not the solution (no consensus view)

<u>American foulbrood</u>

- No treatment is wanted – destruction of infected colonies, shook swarm method

<u>European foulbrood</u>

- No consensus view could be reached on the approach for treatment. In general it was agreed considered that prophylaxis is the key. Many considered that antibiotics were not the solution for the treatment of the European Foulbrood, however this view was not shared by others.

Tropilaelaps

- Treatment options available are considered sufficient at present: the use of treatment as for varroa is recommended,

Small hive beetle

- Veterinary medicines are available based on coumaphos – Adequate in the short term
- More treatment options are needed in long term, particularly for southern countries

Bee viruses

- Essentially linked to the control of varroa
- No need for specific medicines

d) Identify possible reasons for lack of treatment options

As possible reasons for lack of treatment options were identified:

- Resistance problems with existing products
- Efficacy problems
- Incorrect treatment
- Lack of harmonised treatment strategy
- Availability of medicines
- Insufficient knowledge of beekeepers
- High costs of veterinary medicines (vs bulk chemical/homemade product)

- Proposals for possible solutions / actions

The group considered that an overall strategy has to come first to decide case by case whether medication should be used, in which conditions e.g. as last resort. Furthermore, the group considered that:

- Products should be authorised as veterinary medicines to ensure that they are adequately formulated to the intended use.
- Easier registration of medicines of substances with MRLs, especially for the ones that do not require an MRL value (former Annex II substances) – Harmonisation in approach between Member States was considered essential.
- Optimising the use of the substances already available with more flexibility for changing formulation and conditions of use e.g. organic acids
- Further research is needed for development of new/alternative treatments
- Better instructions for appropriate use of the products
- Creation of a group of experts to propose a strategy for treatment
- Control programmes are needed that include good beekeeping practice and medicines

On the reasons described above no proposals for essential substances were made.

Group 2, chair: Dr J.-G. Beechinor (Irish Medicines Board), rapporteur: K Grein/I Koudouna (EMA)

Group 2 was asked to consider more issues of feasibility and to prepare proposals that would help support the use of authorised veterinary medicines by beekeepers instead of relying on chemical substances/own preparations, as it is often current practice. The proposals should address availability of existing authorised veterinary medicinal products as well as development of new medicines (entirely new molecules or substances with MRLs [with or without MRL for honey, substances not requiring an MRL value (former Annex II substances)].

The general conclusions of the group regarding availability of medicines, considering also the concerns identified regarding the access of beekeepers to authorised medicines (need for veterinary prescription), the price of medicines and inadequacy of information on existing products, were:

- Beekeepers must have access to authorised veterinary medicines and have a choice.
- Better communication and information of beekeepers of good beekeeping practice is necessary.
- Adequate information to beekeepers and/or training should be provided to ensure correct use of veterinary medicinal products. This was seen as a role of governments.
- In order to optimise the use of existing veterinary medicinal products, a strategy on what, when and how to use veterinary medicinal products should be established, e.g. on national level, and communicated/published. As example was given that advice on how to alternate varroa medication in summer vs winter should be prepared and disseminated.
- It should be further discussed if countries should provide support, e.g. financial support or national information centres.
- It should also be explored if specific training of veterinarians on bee diseases could be provided.
- It was also considered important that certain veterinary medicinal products could be exempt from prescription to facilitate access to them for the beekeepers.
- It was pointed out that at present several important substances for bee treatment were not available as veterinary medicines, but only available as raw material (used in "homemade" preparations) and without advice for adequate treatment, presents a major obstacle for the use of authorised medicines and development of new ones.

The non-availability of medicines arising from the situation that while a number of veterinary medicinal products are authorised in the EU, they are not accessible to beekeepers across the EU as the marketing authorisations exist only in some countries was further reviewed.

How can existing marketing authorisations be extended to other countries across EU?

- In order to make better use of existing marketing authorisations for bee medicines, it was proposed to explore possibilities under Art 7 of Directive 2001/82/EC, to accept marketing authorisations of other countries.
- The meeting also called for a single EU decision on applications (referred to in the discussion as "automatic mutual recognition"), which is not possible under the current legislation except for centralised applications, but should be explored for a future revision of the legislation.
- Provide incentives to encourage marketing authorisations for bee medicines, e.g. fee waivers, as already done in some countries.

The group discussed if the use of cascade would provide the solution to the problem of (inadequate) availability of medicines?

- The cascade was considered not the preferable solution, as veterinarians need to be consulted, thus making treatment expensive and impractical.
- Furthermore, the veterinarian cannot have the data and knowledge to advise on a withdrawal period.
- Other obstacles: cascade provisions are for exceptional use, it is required to have an MRL for a substance to be used under the cascade; it is also necessary to have an MRL in honey to allow for residue control.
- Positive: Cascade allows the use of veterinary medicines for bees authorised in other countries

Regarding the development of new veterinary medicinal products for bees the group considered that:

- The development of the medicine would have a better chance if an MRL is already available or would be based on the extension of existing MRLs to honey. Such a medicine is considered to have more chance than an entirely new molecule (without MRL).
- The example of oxalic acid was considered a good model to develop a medicine, with MRL as first step. Recognising that the marketing authorisation had so far no economic success, this should however not discourage the application of this model again in the future.
- The review of substances with JECFA/Codex MRLs was encouraged in order to identify if there are potential candidates for bee medicines.
- Regarding new molecules, some substances used in plant protection could be potential candidates.

What incentives for the animal health industry would allow new veterinary medicinal products for bees to be brought on the market? (in place: fee reduction, 13 years data protection, MUMS requirements)

- Data protection is key: 13 years protection is considered adequate, must be unique for formulation. However, this data protection applies only for new products, and is not applicable for extensions under the current legislation. The 5 year window for extensions should be omitted in the future legislation. In addition, the absence of data protection for MRLs is a concern.
- The access to the medicinal products for beekeepers should be facilitated, therefore where possible non prescription medicines should be authorised for bees.
- As a result, centralised marketing authorisations are not suitable as they lead to prescription only medicines.
- It was recognised that the uncertainty on data requirements can be overcome by scientific advice: this is provided free of charge for MUMS products by the European Medicines Agency.
- Another issue considered difficult: The establishment of a withdrawal period for veterinary medicines for bees due to the fact that there is no drug metabolism in honey.

11. Conclusions and recommendations

The presentations and discussions confirmed that the problem of bee health and appropriate treatment of bees is much more complex and diverse than simply identifying some potentially needed medicines.

The conclusions of the breakout sessions were in general supported.

It was reiterated that an overall strategy regarding medicines for bees would need to be established as priority. Such a strategy should identify for each bee disease whether medication was appropriate, and if confirmed, which medication should be used and the appropriate conditions of use clarified.

It was considered essential to improve the knowledge of beekeepers on good beekeeping practice, and that adequate information and/or training should be provided to ensure correct use of medicines. This was seen as a role of governments. It should also be explored if specific training of veterinarians on bee diseases could be provided. Control programmes are needed that include good beekeeping practice and medicines.

It was reiterated that the use of only authorised veterinary medicines for beekeeping should be the goal. Chemical substances used for the treatment of bee diseases should be authorised as veterinary medicines to ensure that they are adequate for the intended use and the correct conditions of use are specified. It was pointed out that at present several important substances for bee treatment are not available as veterinary medicines, but are only available as raw material, used in "homemade" preparations and without advice for adequate treatment presents a major obstacle for the use of authorised medicines and development of new ones.

Another major obstacle to the access to bee medicines by beekeepers was that they are mostly prescription only, requiring consultation of a veterinarian thus making treatment complicated and expensive. While the correct diagnosis of the problem was considered important the proposal was also discussed whether certain veterinary medicinal products for bees could be exempt from prescription to facilitate access to them for the beekeepers.

It was recognised that several veterinary medicinal products are authorised in some Member States in the EU, however they are not authorised and accessible to beekeepers across the EU and in all countries. Efforts should be made to make better use of existing marketing authorisations for bee medicines, and existing legal provisions should be explored, such as Art 7 of Directive 2001/82/EC, marketing authorisations of other countries can be accepted if 'the health situation requires it'. Providing incentives for marketing authorisations for bee medicines e.g. through fee waivers, should also be explored. The use of the cascade was not considered the preferable solution at present due to the limitations that its use imposes. In the future revision of the veterinary legislation further facilitation of marketing authorisations for medicines for bees, e.g. the possibility for a single EU decision for authorisation (referred to in the discussions as "automatic mutual recognition"), should be considered. More flexibility for changing the formulation and conditions of use would also be helpful.

While further research is needed for the development of new/alternative treatment options on the reasons described above no proposals for essential substances were made at this point. It was proposed that an expert group be created to prepare a proposal for a treatment strategy.

Regarding the development of new veterinary medicinal products for bees the meeting considered that in general substances with an existing marketing authorisation for other species and substances with existing MRL or not requiring an MRL (former Annex II substances) would have better chances to reach a marketing authorisation than an entirely new molecule (without MRL). The model for oxalic acid, in which sorting out the MRL was the first step and the collaborative approach between several partners should be further explored for the future.

The animal health industry has shown interest in developing medicines for bees, however it also highlighted the obstacles that hinder medicines development and marketing for bees. Experience has shown that existing veterinary medicines may not be economically successful to allow further investment, as beekeepers continue using raw material or home made preparations. In order to develop new medicines incentives, in particular adequate data protection would be needed.

The meeting considered that continued discussions were necessary to find solutions. It was recognised that many of these aspects of the debate are outside the scope and mandate of the European Medicines Agency, and that further discussions would need to involve additional partners. The efforts by the Agency to organise the meeting and allow these discussions were appreciated and further activities welcomed. The chair thanked the speakers and participants for their contributions and active participation. The Agency will consider if further meetings aimed to continue catalysing the dialogue could be organised.

List of Participants

Agede, Guillaume	CEVA Santé Animale FRANCE
Beechinor, J Gabriel	Irish Medicines Board, IRELAND
Besana, Andrea	COPA COGECA BELGIUM
Branner, Sven	Danish Beekeepers Association DENMARK
Bruneau, Etienne	COPA-COGECA BELGIUM
Cakstina, Andra	Zāļu valsts aģentūra LATVIA
Casimiro, Ramiro	Agencia Española de Medicamentos y Productos Sanitarios SPAIN
Chauzat, Marie-Pierre	Agence Francaise De Securite Sanitaire Des Produits De Sante FRANCE
Chobotová, Eva	Ústav štátnej kontroly veterinárnych biopreparátov a liečiv SLOVAK REPUBLIC
Clayton, Rick	International Federation for Animal Health (Europe) BELGIUM
Clayton, William	Volunteer assisting the Bees for Development organisation UNITED KINGDOM
Clemence, Rick	Pfizer Ltd UNITED KINGDOM
Cyrus, Barbara	European Medicines Agency (EMA) UNITED KINGDOM
De Ridder, Erik	Elanco Animal Health BELGIUM
Draghici, Alina	Institutul pentru Controlul Produselor Biologice si Medicamentelor de Uz Veterinar; ROMANIA
Duarte, Isaura	European Medicines Agency (EMA) UNITED KINGDOM
Dubna, Sona	Czech University of Life Sciences CZECH REPUBLIC
Fehervari, Monika	Central Agricultural Office HUNGARY
Filodda, Frank	Fédération Européenne Des Emballeurs Et Distributeurs De Miel (FEEDM); GERMANY
Gisler, Simon	Andermah Biovet GmbH GERMANY
Grant, James	Fédération Européenne Des Emballeurs Et Distributeurs De Miel GERMANY
Grein, Kornelia	European Medicines Agency (EMA) UNITED KINGDOM
Gurgulova, Kalinka	National Diagnostic & Research Veterinary Medical Institute BULGARIA

Haefeker, Walter	European Professional Beekeepers Association (EBKA) GERMANY
Hahn, Gesine	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit GERMANY
Heck, Thomas	British Honey Association UNITED KINGDOM
Hederová, Judita	Ústav štátnej kontroly veterinárnych biopreparátov a liečiv SLOVAK REPUBLIC
Ionescu, Giusepe	AMC Property ROMANIA
Jencic, Vlasta	Veterinary Faculty university of Ljubljana SLOVENIA
Jones, Anne	Birch Garth (Veterinary Consultant) UNITED KINGDOM
Kay, Jack	Veterinary Medicines Directorate (VMD) UNITED KINGDOM
Kirke, David	ERA Consulting UNITED KINGDOM
Kryger, Per	Aarhus University DENMARK
Lecompte, Philipe	Reseau Biodiversite Pour le Abeilles FRANCE
Liege, Philippe	Anisteme Biosciences FRANCE
Lovett, Tim	British Beekeepers Association UNITED KINGDOM
Maček, Laura	Javna agencija Republike Slovenije za zdravila in medicinske pripomočke; SLOVENIA
Martin, Peter	Honey International Packers Association (HIPA) UNITED KINGDOM
McIntosh, Liz	Food and Environment Research Agency (FERA) UNITED KINGDOM
Neeser, Rosmarie	Swissmedic - Schweizerisches Heilmittelinstitut SWITZERLAND
Orantes Bermejo, Francisco José	CR. Dop Miel de Granada SPAIN
Ponte, Maria Helena	Direcção-Geral de Veterinária (DGV) PORTUGAL
Reybroeck, Wim	ILVO - T & V BELGIUM
Richardson, Jane	European Food Safety Authority (EFSA) ITALY
Rickwood, Sandra	Surrey Beekeepers Association UNITED KINGDOM
Ritter, Wolfgang	OIE Reference Laboratory at CVUA GERMANY
Schuermann, Annette	Bayer Cropscience AG GERMANY

Seinhorst, Jan Willem	Central Veterinary Institute of Wageningen UR NETHERLANDS
Sharman, Matthew	Food and Environment Research Agency (FERA) UNITED KINGDOM
Siefert, Benoit	VETO PHARMA FRANCE
Simón Delso, Noa	Centre Apicole de Recherche et d'Information (*C.A.R.I.*) BELGIUM
Soto, Emma	European CommissionDG General Health and Consumers BELGIUM
Spagnuolo-Weaver, Martha	Veterinary Medicines Directorate (VMD) UNITED KINGDOM
Stanchev, Philip	Primavet-Sofia Ltd BULGARIA
Tervell, Margareta	Swedish Board of Agriculture SWEDEN
Torres Fernandes Pinas, Cristina	C.R. Protected Designation Origen Honey of Granada SPAIN
Trumpickaitë Dzekèiorienë, Snieguolë	Nacionalinis maisto ir veterinarijos rizikos vertinimo institutes; LITHUANIA
Tsigouri, Angeliki	National Organisation for Medicines (EOF); GREECE
Vandaele, Bill	Klifovet BVD; Association of veterinary Consultants (AVC) BELGIUM
Vernerova, Eva	Ústav pro státní kontrolu veterinárních biopreparátů a léčiv CZECH REPUBLIC
Vidal-Naquet, Nicolas	Federation of Veterinarians of Europe FRANCE
Voichita, Andrei	Tapas srl ROMANIA
Watkins, Max	Vita (Europe) Limited UNITED KINGDOM
Wilkins, Selwyn	National Bee Unit (NBU) UNITED KINGDOM