The use of drugs to control varroosis in honeybee colonies and
European legislation– the current situation

Introduction

In an attempt to harmonise the manufacturing, production and use of medicinal products the European Union has produced a considerable amount of legislative documents which apply to Member States.


Regulations 2377/90 and 434/97 require that the maximum tolerable amounts of residues – the so-called "MRL-value" of pharmacologically effective substances from veterinary drugs in foodstuffs and, therefore, in honey must be determined by the European Agency for the Evaluation of Medicinal Products (EMEA). Noteworthy is that the MRL refers only to the animal species and the types of foodstuff for which it has been requested. Since January 1, 2000, the use of pharmacologically effective substances lacking an MRL has been illegal in the European Union. With reference to honey, it bans all veterinary drug residues except those that have been previously approved. Due to changes in legislation, mostly concerning the avoidance of residues in
foodstuff, numerous drugs used to control varroosis in bees caused by *Varroa destuctor* (old designation: *Varroa jacobsoni*) are no longer available. Within the European Union only a limited number of therapeutic drugs for this use are still on the market, and the possibility of using them against varroosis is reduced as the parasite has developed resistance to some of the approved drugs, while others are of difficult application. Resistance has already been shown against tau-fluvalinate, flumetrin and, more recently, also against coumaphos. We are going to have emergency conditions concerning Varroa control.

A document that seems to conflict with the above-mentioned rules concerning MRL and approval of drugs is Council Regulation (EC) 1804/1999 of July 19, 1999 supplementing Regulation (EEC) 2092/91 on organic production of agricultural products and indications referring thereto on agricultural products and foodstuffs, including livestock production.

Paragraph "6. Disease prevention and veterinary treatments" states as follows: "6.3. The use of veterinary medicinal products in beekeeping which comply with this regulation shall respect the following principles:

a) they can be used so far as the corresponding use is authorized in the Member State in accordance with the relevant Community provisions or national provisions in conformity with Community law;

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(e) without prejudice to the principle in (a) above, formic acid, lactic acid, acetic acid and oxalic acid and the following substances: menthol, thymol, eucalyptol and camphor can be used in cases of infestation with Varroa jacobsoni.

Paragraph 6.3, letter e) seems to allow the possibility of using the substances listed for the control of the Varroa mite regardless of the EU licensing rules. In fact, this is the first time such a statement has been included in an official document. It should be emphasized that although limited to organic production, this statement could represent the missing legislative basis for integrated control of this parasitic disease as required by most research institutes in Europe for the future.

Conflicting regulations

EU regulations are legally in force in all Member States beginning on date of their publication. Implementation as national law is not required by Member States. Council Regulation (EC) 1804/1999 is in conflict with the previously-mentioned EU regulations concerning MRLs. Furthermore, it deals only with organic farming (here, specifically with beekeeping) and contradicts equality principles. In fact, it is not reasonable to have a therapeutic treatment approved for organic farming [beekeeping] and the same treatment forbidden by the law
currently in force, when the same treatment applied to “conventional” farming. However, according to information provided by the EU authorities on request, the legal requirement in Member States remains the following: as a matter of principle, new drugs require either a national or an European approval on the basis of an MRL-assessment in spite of Council Regulation (EC) 1804/1999.

**Legalisation of ethereal oils and organic acids**

Up to now, most of the ethereal oils and organic acids mentioned in Council Regulation (EC) 1804/1999 are indeed prohibited. It will be urgently necessary to legalize substances in these classes as drugs for veterinary use. They were developed by independent research institutes to the point where they could be used as drugs to prevent an emergency condition concerning Varroa control. New substances cannot be expected from the pharmaceutical industry, due to the high developmental and approval costs for the market of bee drugs, which is considered a “niche” market. Furthermore the substances mentioned above are cheaply available for other purposes. In the future, drugs for honeybees will, in most cases, most likely come from research projects performed in public institutions.

For application and use of new drugs, there are two possibilities within the EU for licensing a medicament:
1. national approval for one country, with the possibility of implementing national approval from another European Union member state;

2. central approval for all EU member countries.

However, the approval process may only be initiated by pharmaceutical companies. Independent research institutes have limited possibilities for obtaining approval of the substances they have developed.

Independent research institutes may only make use of national regulations still in force in some countries, for example: in Germany the "Standard Approval" and in Austria the "Approval as a auxiliary substance". However, these authorisations cannot be used by other European Union Member States.

Since the honeybee, as a pollinator, is so important for preserving environmental balance, and in view of the possible “state of emergency” regarding parasite treatment, EC task force CA 3686, composed of scientists from Member States and non-member countries, began its work in 1998, aiming to develop integrated strategies in varroosis treatment. An essential part of this action is the development of treatment protocols using organic acids and ethereal oils which are considered valid alternative drugs, mainly for two reasons. Firstly, they can replace the “hard” chemical drugs that, because of the resistance they induce in parasites, are of limited effectiveness. Secondly, they guarantee a low residue level, if any, in honeybee products. In trials performed
In several European countries, e.g. oxalic acid and thymol were applied and shown to be highly effective, but a clear European legislative basis for the integrated control of varroosis is still missing.

In the European Union, the conflicting regulations mentioned above are dealt with in various ways: the use of organic acids and ethereal oils is, in some cases, forbidden, in others tolerated or even ignored by the designated authorities in many European countries.

In Austria formic acid, lactic acid, oxalic acid and thymol are not registered as medicaments, but as auxiliary substances, which can be used as preventive drugs to keep the bees healthy.

In Switzerland (not a member state of the EU), formic acid, lactic acid, oxalic acid and thymol are registered also as auxiliary substances, supplementary formic acid is registered as a medicament under the trade marks Illertisser mite plate and Krämer plate, thymol under the trade mark Apiguard.

A proprietary medicinal product, ApilifeVAR, containing four ethereal oils, i.e. thymol, menthol, eucalyptol and camphor, previously authorised as antiparasitary drug for external use has been registered in Italy in December 2000. Apiguard, containing thymol as active ingredient, has obtained the same registration in 2003.
In Germany, formic acid was legalized in the application form of short term evaporation (Illertisser mite plate) and via standard approval in the application form of long term evaporation (Nassenheider Evaporator) as a medicament. Lactic acid is still under consideration but officially tolerated up to the end of the approval procedure.

For Thymovar, active ingredient thymol, a standard approval procedure has been started. The approval process for Apiguard (also Thymol) was completed in November 2002.

For oxalic acid, a substance with very high acaricidal potential, the institutes carrying out the approval process face complex problems. Oxalic acid is a substance for which no MRL has yet been established. Without an MRL, national registration is impossible in all European Member States. Since determining an MRL is complex and expensive, it is unclear whether approval can be obtained by research institutes, which have no financial resources for tasks like licensing procedures.

After an MRL has been established, national approval for that substance must be applied for and obtained. Institutes are not enabled to request central approval, even if a medicinal product is required all over Europe. Generally, establishing the MRL and obtaining approval are matters carried out by the
pharmaceutical industry. However, in the case of oxalic acid, the cost-benefit ratio is extremely low, due to the limited market that honeybees represent.

**Conclusions**

Honeybees are an example of a “minor species” of high importance to human beings, but of very low commercial interest to the pharmaceutical industry. EMEA is aware of this situation of the so-called “minor animal species” -the lack of veterinary medicinal products and the increase of off-label use of products or substances- and is seeking a solution. Two EU “Notes for Guidance” could be useful in making substances available for use as drugs in minor animal species:

1. Note for Guidance on the Establishment of Maximum Residue Limit for Minor Animal Species, date for coming effective November, 12th, 1997;


When a substance is included in Annex I, II or III of Council Regulation (EEC) 2377/90 the extrapolation from so-called “major species” such as sheep, cattle, chickens etc. to “minor species” (horse, rabbit etc.) can be made. The
target tissues of the corresponding major and minor species of food-producing animals should be the same. A substance which is not already assessed for a major species and determined exclusively for use in a minor species can be evaluated by an abbreviated data package for assessing its toxicity.

But these Notes for Guidance cannot solve the problems of the lack of drugs for honeybees, although honeybees are not specifically mentioned in them, and it is difficult or impossible to extrapolate residue values from other foodstuffs to honey. There is no chance here to make the required medicaments available. For bees the following steps are needed in order to allow scientific institutes to provide the urgently needed drugs:

1. In case of public importance the procedures of establishing the MRLs and for registering the drugs for bees must be simplified

2. Application fee must be reduced even if some drugs are available. Due to bee and parasite biology different drugs, applied at different times of the years, are unequivocally required.

3. Financial support for rare diseases with public importance such as from the “Orphan drug” fund in the USA, is available in Europe only for human drugs, not for veterinary medicaments.
Highly effective legalized acaricides are urgently needed to keep the parasite under the damage limit and to make sure that bee colonies survive varroosis.

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