EUROPEAN LEGISLATION GOVERNING THE AUTHORISATION OF VETERINARY MEDICINAL PRODUCTS WITH PARTICULAR REFERENCE TO THE USE OF DRUGS FOR THE CONTROL OF HONEY BEE DISEASES

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Summary

With the adoption of the new authorisation system, the European Union has stated all its regulatory requirements for veterinary medicinal products. This system gives innovative products access to a continent-wide market and facilitates access for other products to the Member States' markets. Medicines used for the control of Varroa destructor infestation and of other diseases in honeybee are also regulated by this authorisation system.

European Community pharmaceutical legislation covers medicinal products for both human and veterinary use. Harmonisation of requirements in the veterinary medicine area began with the adoption of Directives 81/851/EEC and 81/852/EEC, which laid down common requirements for manufacturing and marketing authorisations, based on evaluations of the quality, safety and efficacy of the product.

However, authorisations were granted on a national basis. As a consequence, the Member States made different decisions on individual products. For this reason the commission proposed a new system for licensing medicinal products, which was adopted by the Council of Ministers in 1993 and went into force on January 1, 1995. One of the first consequences was the creation of the European Agency for the Evaluation of Medicinal Products (EMEA) in London.

EMEA, on the basis of Council Regulation (EEC) 2377/90, laid down a Community procedure for the establishment of Maximum Residue Limits (MRLs) of veterinary medicinal products in foodstuffs of animal origin, banning all veterinary drug residues in honey, with the exception of those substances already approved.

Since EMEA was establishment in 1995, two new registration procedures for human and veterinary medicinal products became available through the EU: the centralised and the decentralised (mutual recognition) procedures. In accordance with Directive 81/851/EEC, authorisation is also required for the manufacture of veterinary medicinal products.

The EMEA maintains close contacts with the licensing authorities of the European Economic Area, in which integration is developing via the implementation of common directives and guidelines of medicines for human and veterinary use. The European Pharmacopoeia co-founded, along with the Japanese Pharmacopoeia and the United States Pharmacopoeia, the Pharmacopoeial Discussion Group (PDG) in 1990.

Here we present the current situation in the pharmaceutical marketplace, after implementation of European Union pharmaceutical legislation concerning drugs used in bees colonies to control Varroosis. We present an overview using one of the member states, Germany, as an example. The problems involved in a coordinated effort within the European Union are exemplified by organic acids and ethereal oils. A special mention is made of the Council Regulation (EC) 1804/1999 of July 19, 1999 on organic production of agricultural products, including products used in bee colonies. In fact, it appears to allow the possibility of using a list of substances for the control of Varroa mites, regardless of the EU licensing rules. Here it is urgently necessary to reach a clear agreement on a European Union level. Furthermore, no antibacterial drugs are currently authorised in the EU for the control of American foulbrood, European foulbrood as well as Nosema apis.

The authorization of pharmaceutical products on the basis of their MRL, in accordance with regulations of the European Community, poses a problem for those classes of animals that are of minimal commercial interest to the pharmaceutical industry, such as bees. For varroosis we can conceive a 'state of emergency' regarding treatment, if, following EU legislation, no solutions are found that also include bees as a 'minor species'. This is all the more important, because the necessary medicaments used with bees, resulting from research institutes in the task force funded by the EU to develop new treatments, still lack an unambiguous legal footing for the integrated treatment strategies that have been discovered.

Introduction

European Community pharmaceutical legislation, which has evolved over a 30-year period, covers medicinal products for both human and veterinary use. Harmonisation of the requirements in the area of veterinary medicine began in 1981 with the adoption of Directives 81/851/EEC and 81/852/EEC, which laid down common requirements for manufacturing and marketing authorisation of products based on the quality, safety and efficacy. Additional measures were subsequently taken to further harmonise procedures and criteria for the evaluation of veterinary medicinal products. Among them, framework requirements and interpretative indications for their testing, and principles and guidelines of Good Manufacturing Practice (GMP), were established, together with a community procedure for the evaluation of high-technology products (Pastoret and Falize, 1999).

However, authorisations were still being granted on a national level. As a consequence, although applications were evaluated on the basis of harmonised criteria and procedures, and in some cases were obtained jointly by Member States, different decisions were still being made on individual products. For this reason in 1990 the commission proposed a new system for marketing authorisation of medicinal products, which was adopted by the Council of Ministers in 1993 and went into force on January 1, 1995.

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European Agency for the Evaluation of Medicinal Products (EMEA)

In 1995 a new European system for the authorisation of medicinal products came into force. After ten years of co-operation between national registration authorities at the European Union (EU) level and four years of negotiations, in June 1993 the Council of the EU adopted three directives and one regulation, which together form the legal basis of the system (Brunko, 1997).

The EMEA was established by Council Regulation (EEC) 2309/93 of July 22, 1993 (OJEC L214, 24.8.1993) and London was chosen as its seat.

The EMEA mission statement is to contribute to the protection of public and animal health by:

- mobilising scientific resources from throughout the EU to provide high quality evaluation of medicinal products, to advise on research and development programmes and to provide useful and clear information to users and health professionals;
- developing efficient and transparent procedures to allow timely access by users to innovative medicines through a single European marketing authorisation;
- controlling the safety of medicines for humans and animals, in particular through a pharmacovigilance network and the establishment of safety limits for residues in food-producing animals.

This agency formulates opinions and, apart from the administrative staff and the management board, is composed of two scientific committees, the CPMP (Committee for Proprietary Medicinal Products) in charge of medicinal products for humans and the CVMP (Committee for Veterinary Medicinal Products) in charge of the animal health division.

The CVMP is responsible for the marketing authorisation for products derived from biotechnology, for growth promoters, new chemical compounds intended for use in food-producing animals, and other innovative products. In addition, the CVMP makes recommendations according to Council Regulation (EEC) 2377/90 of June 26, 1990 (OJEC L224, 18.8.1990) on MRLs (Maximum Residue Limits) for each substance used in food-producing animals.

The CVMP has appointed the following working groups chaired by some of its members: residue safety; efficacy; immunological veterinary medicinal products; pharmacovigilance; and joint CPMP/CVMP quality. Considerable effort has also been put into developing guidance indications on a variety of topics.

Transparency is a major objective of the agency, and is achieved by publishing European Public Assessment Reports (EPARs) for all centrally approved products on the EMEA's web page (http://www.eudra.org/). Furthermore, the web page also contains Summary Reports for Maximum Residue Limits for Veterinary Medicines for food animals and provides information to the public on the steps undertaken by the Agency's Secretariat and its Scientific Committees (Jones, 1999).

To support its activities, the CVMP relies on group of 400 experts among the over 2000 now accredited, at the service of the agency on behalf of the EU Member States.

The guidelines for testing veterinary medicinal products are contained within Volume VII of the collection of rules governing medicinal products in the EU, published by the European Commission in 1994.

Maximum Residue Limits (MRLs)

Council Regulation (EEC) 2377/90 laid down a Community procedure for the establishment of MRLs for veterinary medicinal products in foodstuffs of animal origin.

In order to be placed on the market, a medicinal product must receive a Marketing Authorisation (previously named Product License) complying with the EC Medicines Legislation. An application to the competent authorities must include evidence of efficacy and safety, toxicological studies and metabolic and residue studies. Obviously, these studies must be performed on the commercial product, thus including data on the active chemical and on the excipient.

A similar system for medicinal product approval was in place in Member States before the creation of the EMEA. In fact, all products on the market in January 1992, which contained as an active compound, a substance included in the "list of defendable substances" (Communication of the EMEA pursuant to art. 1 of the Council Regulation (EC) 434/97; OJEC C165, vol. 40, 31.5.1997) could legally stay on the market until the end of 1999. By December 31, 1999 it was required that the pharmacologically active substances be included in Annex I, II or III of Council Regulation (EEC) 2377/90 or the product would be withdrawn from the market. Inclusion in the annexes mentioned can be obtained via an official application to establish the product’s MRL.

Available European Licensing Procedures

Since 1995, two new registration procedures for human and veterinary medicinal products have become available through the EU: the centralised and the decentralised procedures.

The centralised procedure is compulsory for medicinal products derived from biotechnology (Part A of the annex to Regulation 2309/93), and is available by request for other innovative products (Part B of the annex to the same regulation) (Table 1). Applications are submitted directly to the agency in London. At the conclusion of the scientific evaluation undertaken in 210 days within the agency, the Scientific Committee's opinion is transmitted to the commission, where, within an additional 90 days, it will be transformed into a single market authorisation applying to the whole EU. Applications may be submitted following either Part A or of Part B of the annex.

Article 3 of Regulation 2309/93 (which established EMEA) states that no medicinal product referred to in Part A of the annex may be placed on the market without undergoing the centralised procedure. Conversely, for licensing a medicinal product referred to in Part B of the annex, the centralised procedure may be requested but is not compulsory.

The decentralised procedure, applying to the majority of conventional medicinal products, is based on the principle of mutual recognition of national authorisations. It implies for the extension of marketing authorisation granted by one Member State to one or more other Member States identified by the applicant. Should other Member States not recognise the original national authorisation, the points in dispute are to be submitted to the agency's scientific committees for arbitration. In this case, the European Commission adopts the final decision with the assistance of the regulatory committee or, in the event of complete disagreement between the Member States, by the Council of the EU.

Member States recently created a Mutual Recognition Facilitation Group (MRFG) in order to facilitate the admission of medicinal products under the decentralised procedure. Meetings are being held monthly at the EMEA and are chaired by the United Kingdom.

Other national procedures remained available to applicants in different European countries, but the products could then be used only in the national market (for example, in Germany the so-called "Standardzulassung").

Manufacturing Authorisation

In accordance with Directive 81/851/EEC, authorisation is also required for manufacturing veterinary medicinal products. This directive requires regular inspections and that manufacturing procedures must be supervised by a "qualified person", who certifies that each batch complies with the approved specifications of the product. For the implementation of these requirements, the commission has adopted Directive 91/412/EEC relating to the principle and guidelines of Good Manufacturing Practice (GMP), and published a detailed guide on GMP, developed by a group of pharmaceutical inspectors of the Member States.

European Pharmacopoeia

Thirty years ago, each country had its own licensing regulations, and between them the European countries had two-thirds of the world's pharmacopoeias. The European Pharmacopoeia Convention has now been signed by 24 parties: 23 countries and, recently by the Commission of the European Communities. Moreover, 10 European and non-European countries and the World Health Organisation (WHO) have observer status. EMEA maintains close relationship with the licensing authorities of the European Economic Area, where integration is developing via the implementation of common directives and guidelines for medicines intended for human and veterinary use. In 1990 the European Pharmacopoeia co-founded, along with the Japanese Pharmacopoeia and the United States Pharmacopoeia, the Pharmacopoeial Discussion Group (PDG). This group is working steadily toward harmonisation on a world level (Artiges, 1997).

During the 1960s in Europe, it was agreed (mainly within the framework of two major international organisations, the EU and the Council of Europe) to pool technical and scientific expertise. This led to the development of a coherent body of regulations covering marketing and quality control of medicines for human and veterinary use. Its main contents are marketing authorisation procedures granted singularly for medicines

manufactured industrially, and the Pharmacopoeia, a tool for standardisation. The European Economic Community elaborated the regulations concerning marketing authorisation after extensive public consultations with professional pharmaceutical associations as well as the European Free Trade Association (EFTA) countries and the Nordic countries. The European Pharmacopoeia was developed under the *aegis* of the Council of Europe by means of a specific international convention, which from the beginning allowed numerous European countries to participate.

The convention on the Elaboration of a European Pharmacopoeia is based on a dual commitment by its signatory states:

- to elaborate a common pharmacopoeia, by contributing to its budget and by guaranteeing experts articipation;
- to promote the gradual replacement of the national requirements with the specifications of the European Pharmacopoeia.

This commitment has been made official and integrated into the regulations for the registration of medicines manufactured industrially since the adoption in 1975 of the first directive (75/318/EEC) on the standards and protocols for analytical, pharmacotoxicological and clinical studies on medicines for human use. This principle has also been applied in the area of drugs for veterinary use according to Directive 81/852/EEC. Subsequently, these requirements were extended to immunologic products (Directive 89/342/EEC), to veterinary vaccines (Directive 90/677/EEC), and to homeopathic medicines for human (Directive 92/73/EEC) and veterinary use (Directive 92/74/EEC).

Veterinary medicinal products in bee colonies to control varroosis and other diseases – the current situation

Concerning bees, three European Community regulations are most relevant: Council Regulation (EEC) 2377/90, (EC) 434/97 and (EC) 1804/99. Regulations Nos. 2377/90 and 434/97 require that the maximum tolerable amounts of residues - the "MRL-value" of pharmacologically effective substances from veterinary drugs in foodstuffs and, accordingly, for honey - be determined by the European Agency for the Evaluation of Medicinal Products (EMEA, see before). The MRL refers only to the animal species and the type of foodstuff for which it has been required. From January 1, 2000 on, the use of pharmacologically effective substances lacking an MRL is illegal. With reference to honey, it bans all veterinary drug residues except those that have been approved (Martin, 1999). Table 2 contains the list of chemicals authorised by EMEA for use in fighting bee diseases.

Since establishing a database for evaluation of a substance for veterinary use is complex, and since the determination of an MRL by the EMEA is expensive, no MRLs have been set for various substances previously used as medicaments in the member states. Due to the changes in legislation, mostly concerning the avoidance of residues in foodstuff, numerous drugs for bees are no longer available. Table 3 presents the situation in Germany as an example for the situation. Many of the preparations previously used to fight varroosis are no longer ad command. European wide only a few therapeutic drugs are still on the market for this use, and this number is further reduced

as the parasite develops resistance to most of the approved drugs (listed here). Resistance has been shown against Apistan, Bayvarol, and Perizin. Table 4 summarizes the products used in European countries for varroosis treatment. Column 3 shows those which have gone through the MRL-procedure and through the registration procedure as veterinary medicine.

In apparent contrast to 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 (OJEC L222, 24.8.1999).

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 listed substances 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.

EU regulations are legally binding in all member countries from their publication date on. Implementation as national law is not required by the member states. This Council Regulation (EC) 1804/1999 from the area of agriculture conflicts with the previously-mentioned EU regulations from the health field concerning MRLs. Furthermore, it deals only with ecological farming (here, specifically with beekeeping) and contradicts equality principles. After being legally reviewed by the German Federal Ministry of Health, these substances may not be used as drugs without approval (Certificate from the Ministry of December 23, 1999). According to the information provideed by the EU authorities on request, the legal status remains this: as a matter of principle, new drugs require either a national or a European approval on the basis of a MRL-assessment in spite of Council Regulation (EC) 1804/1999.

Up to now, most of the ethereal oils and organic acids mentioned in Council Regulation (EC) 1804/1999 are prohibited without approval, it will be urgently necessary to legalize substances in these classes as drugs ad us vet.. They were developed by independent research institutes, to the point where they could be used as drugs to prevent a state of emergency regarding Varroa control. New substances cannot be expected from the pharmaceutical industry, because developmental and approval costs are too high in the

market for bee drugs, which is a small one. In the future, drugs for bees will, in most cases, come from institutes.

There are two possibilities in the European Union for trying to register a medicament, (see above):

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 severely limited possibilities of obtaining approval for the substances they have developed. Institutes are only able to make use of national special regulations still in force in some countries, for example: in Germany the "Standard Approval" and in Austria the "Approval as a auxiliary substance". These cannot be implemented by other European Community 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, the EC task force CA 8636, composed of scientists from member states, began its work in 1998, aiming to develop integrated strategies in varroosis treatment. An essential part of this is the development of treatment methods using organic acids and ethereal oils which are important for two reasons: they can replace the 'hard' chemical drugs which, because of their resistance, are of limited effectiveness, and they guarantee a small amount of residue, if any, in honeybee products. In the experiments in many European countries, for example, oxalic acid and thymol were developed to the point of full usefulness, but the clear European legislative basis to the integrated control of varroosis is still missing. In the European community, the conflicting regulations are dealt with in various ways: the use of organic acids and ethereal oils is forbidden, tolerated or ignored by the appropriate authorities in many European countries.

In Austria and Switzerland (the latter not a member state of the EU), formic acid, lactic acid, oxalic acid and thymol are registered not as medicaments, but as auxiliary substances, which can be used as preventive drugs to keep the bees healthy. Supplementary in Switzerland formic acid is registered as a drug. In Germany the approval process is either underway or already completed for some substances in the categories mentioned above: formic acid was licensed in 1985 in the "short-term application form" called the "Illertisser mite plate". The "long-term" application form, more effective and very well-tolerated by bees, was approved on July 12, 2000 (Bundesgesetzblatt Teil I, G 5702 Nr. 31) as a so-called "Standard Approval", applied for by the Free University of Berlin. For lactic acid, the "Standard Approval" process was begun in June 1999 by the Free University of Berlin and the German Beekeeper Association, in cooperation with the Mayen Dept. of Bee Research.

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 very recently registered in Italy (Commission Directive 94/40/EC of 22 July 1994).

For thymol, as a well-known therapeutical substance, a pharmaceutical company has begun the approval process seeking approval for four other European countries as well.

Table 4 give an overview of the use of organic acids and ethereal oils and their licensing status in different European countries.

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 reached by research institutes, which have no financial resources for tasks like licensing procedures.

After an MRL has been established, national approval must be applied for. Institutes cannot apply for central approval, even if a medicament is needed all over Europe. Normally, establishing the MRL and obtaining approval are matters carried out by the pharmaceutical industry. In the case of oxalic acid it is uninteresting for the pharmaceutical industry, because the considerable time and expense involved due to the non-existent MRL is out of proportion to the small size of the market. Bees are an example of a "minor animal species" of high importance to human beings but of low interest to the pharmaceutical industry. EMEA is aware of this situation of "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 species:

1. Note for Guidance on the Establishment of Maximum Residue Limit for Minor Animal Species, date for coming into operation November, 12th, 1997
2. Note for Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin, submitted to the CVMP for consultation April 2000, consultation ended in October 2000.

When a substance is included in Annex I, II or III to Council Regulation (EEC) 2377/90 extrapolation from so called "major species" such as sheep, cattle, chicken 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 minor species, can be evaluated by a abbreviated data package for assessing the 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:

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

- 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.

Concerning antibacterial drugs, in the European consultation conference on the availability of veterinary medicinal products “Practical and safe use of veterinary medicines” held in June 1999, it was realized that tetracyclines and sulphonamides are used in the treatment of foulbrood. However, although MRLs have been established for all-food producing species for these two classes of compounds, there are no MRLs for honey. Furthermore, there is no formulation, which is really adapted to the treatment of bees.

In conclusion, highly effective legalized acaricides are urgently needed to keep the parasite under the damage limit and to make sure that bee colonies survive varroosis. On the other hand, the use of antibacterial substances, such as sulfonamides and antibiotics whatever the class, should be discouraged due to the raising presence of residues in honey and other beehive products.

References

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Table 1. Annex to Council Regulation (EEC) n. 2309/93 of 22 July 1993

PART A Medicinal products developed by means of one of the following biotechnological processes:

- recombinant DNA technology,
- controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
- hybridoma and monoclonal antibody methods.

Veterinary medicinal products, including those not derived from biotechnology, intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals.

PART B Medicinal products developed by other biotechnological processes which, in the opinion of the Agency, constitute a significant innovation.

Medicinal products administered by means of new delivery systems which, in the opinion of the Agency, constitute a significant innovation.
Medicinal products presented for an entirely new indication which, in the opinion of the Agency, is of significant therapeutic interest.
Medicinal products based on radio-isotopes which, in the opinion of the Agency, are of significant therapeutic interest.
New medicinal products derived from human blood or human plasma.
Medicinal products the manufacture of which employs processes which, in the opinion of the Agency, demonstrate a significant technical advance such as two-dimensional electrophoresis under micro-gravity.
Medicinal products intended for administration to human beings, containing a new active substance which, on the date of entry into force of this Regulation, was not authorised by any Member State for use in a medicinal product intended for human use.
Veterinary medicinal products intended for use in food-producing animals containing a new active substance which, on the date of entry into force of this Regulation, was not authorised by any Member State for use in food-producing animals.

Table 2. Substances authorised by EMEA and their limits

Veterinary drug	MRL	Foodstuff	Annex	Remarks
Tau-Fluvalinate (Apistan)	-	-	II	none considered necessary
Flumethrin (Bayvarol)	-	-	II	none considered necessary
Formic acid	-	-	II	none considered necessary
Lactic acid	-	-	II	none considered necessary
Menthol	-	-	II	none considered necessary
Thymol	-	-	II	none considered necessary
Eucalyptol	-	-	II	none considered necessary
Camphor	-	-	II	none considered necessary
Mixed oils (ApilifeVAR) [1]	-	-	II	none considered necessary
Cymiazole (Apitol)	1000 ppb	honey	III	provisory MRL (expired on July 1, 2001)
Amitraz (Apivar)	200 ppb	honey	I	definitively determined MRL
Coumaphos (Perizin)	100 ppb	honey	I	definitively determined MRL

[1] A proprietary mixture of the four essential oils listed

Table 3. Medicaments for bees in Germany

Approved medicaments	active substances
Illertisser mite plate	Formic acid
Long-term evaporation (Nassenheider Evaporator)	Formic acid
Perizin	Coumafos
Bayvarol	Flumethrin
Apitol	Cymiazol hydrochloride
Medicaments no longer allowed	
Folbex VA Neu	Brompropylat
Cekafix	Coumafos
Nosemack	Mercury compounds
Fumidil B	Fumagillin
Fumagillin	Fumagillin
Berovacid	Brompropylat

Table 4. Products used in European countries (EU and other countries) for the control of *Varroa destructor* infestation and their licensing status

Country	Registration as pesticide	Registration as veterinary medicine[i]	Registration as auxiliary substance, different trade-marks	Not registered, but accepted/tolerated/temporary authorisation[ii]
Austria		Apistan, Apitol[iii], Perizin	FA, LA, OA, thymol	
Belgium	Apistan	Apivar		OA, FA, LA
Denmark		none		Annex II EC Regulation 2377/90
Finland	Thymol, OA, Apistan, FA[iv]			
France		Apistan, Apivar, Apiguard		Annex II EC Regulation 2377/90
Germany		Apitol, Perizin, , Bayvarol, FA (Nassenheider Evaporator), Illertisser mite plate		
Greece		Apistan, Perizin, Apitol, Folbex		
Hungary	ApilifeVAR, Perizin, Apitol, Apistan			
Italy		ApilifeVAR, Perizin, Apitol, Apistan, Bayvarol, Apivar		FA, LA, OA, thymol
Norway			FA, LA, OA	
Portugal		Apistan, Apivar		
Republic of Ireland		Bayvarol		
Slovenia	Apistan, ApilifeVAR			
Spain		Apistan, Perizin, Apivar		OA, FA, LA, thymol, rotenone
Sweden	Apistan			Essential oils, FA, LA, OA
Switzerland		Apistan, Bayvarol, Perizin, Apitol, Folbex, Illertisser mite plate, Krämer plate	FA, LA, OA, thymol	
The Netherlands		Apistan, Apitol, FA		OA, FA, LA
United Kingdom		Bayvarol, Apistan		FA, thymol, LA

[i] Directives 81/851/EEC, 90/676/EEC, 81/852/EEC, 87/20/EEC, 94/40/EEC, 93/41/EEC.
[ii] This information was kindly supplied by the participants in the Concerted Action 3686 "Coordination in Europe of research on integrated control of *Varroa* mites in honey bee colonies".
[iii] The MRL expired in Juli 2001. The application is not allowed in the EU, but the registration is not yet cancelled.
[iv] Decision made by the pesticide regulation board of Ministry of Agriculture on April 29, 1998: "Products containing formic acid, oxalic acid or essential oils have to be registered as a pesticide, if used in the control of varroosis or acariosis" these products are not allowed to be sold or used, if they are not registered as a pesticide.

FA = formic acid, LA = lactic acid, OA = oxalic acid