Therapeutic gaps in the bee sector

Hearing of 18/12/23

Participants: Samuel Boucher (LABOVET, Chairman of the SNGTV beekeeping commission), Lionel Grisot (Veterinary practitioner in Franche Comté, mandated beekeeping veterinarian for DDPP, member of the CSMV), Florentine Giraud (beekeeping veterinarian, FNOSAD project manager), Stéphanie Franco (Anses – laboratory of Sophia Antipolis, Head of the LNR bee health, veterinarian).
for the ANMV: L. Baduel, B. Leroux, F. Pillet, J. Bietrix, L. Fabry**.**

Reminder of the responsibility for the comments made during the hearing and reported in this report:
- The identification of therapeutic gaps (and details of situations expressed and alternatives considered) is the responsibility of the representatives of the veterinary profession
- The ANMV provides additional information or answers to the technical and regulatory questions addressed. These supplements are systematically preceded by "Info ANMV : … to distinguish the origin of the words expressed.

Table summarising the comments of the representatives of the veterinary profession (*new elements since the last hearing – in blue)*:

Disease	**Problem encountered:** **PhV:** Pharmacovigilance (efficacy or safety perceived as unsatisfactory) **Disp:** Availability, shortage **Reg:** Regulatory (cascade application, withdrawal period, restricted access) **0 VMP:** Absence of appropriate veterinary medicinal products (VMPs) **0 TS:** Lack of therapeutic solution	**Problem Type: PhV, Disp, Reg 0 VMP 0 TS**	**Alternatives identified**	**PRIORITIES** **Major: M** **minor: m**
Varroosis	• **Reduced efficacy and questioning of certain treatments** Lack of efficacy of authorised VMPs, resistance of varroa mites ? Decreases in the efficacy of amitraze recorded by the FNOSAD for several years and even more significant for the efficacy tests carried out in 2022 => Resistance tests via LDA 39 or APINOV were conducted, but are difficult because they require a lot of live varroa mites. Problem because of wide use (except in organic farming) of strips which are the easiest to use. Their use alone, in late-summer treatment, often seems not enough. Different approaches for detecting resistance to acaricides exist: phenotypic or genomic method. Work is underway on methods for detecting these resistances. **LNR:** A method based on a biological test for exposure to tau-fluvalinate and amitraze was implemented by Apinov as part of an academic thesis (see publication: Almecija, 2020). A molecular method for identifying **Varroa's**	PhV	The list of available drugs has been extended with now 16 AMM incl. 2 recent ones: - VARROXAL 0.71g/g: MA in France (*via* Mutual Recognition/MR) dated 08/09/23 and - APIGUARD multidose MA dated 25/03/22 Once resistance detected, return to sensitivity is possible: e.g after 3 to 4 years for tau-fluvalinate. Currently insufficient data to determine this period in the case of amitraze resistance. ⇨ **Wish for rapid diagnostic tests** to determine whether tau-fluvalinate and amitraze are effective and therefore usable. ➢ Communication to stimulate the search for new drugs? We need a new molecule and/or pharmaceutical form of oxalic acid that could be used in the presence of the brood.	**M** **No. 1**

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	genetic resistance to tau-fluvalinate was developed by a Spanish research team (J. Gonzalez). The LNR has begun work to implement the method in 2020. Work is underway to implement/develop a method for detecting the **genetic resistance of Varroa to amitraze**. The LNR is in contact with Apinov and the Spanish researchers on this subject. The results of analyses carried out on French samples show that there is a good correlation for tau-fluvalinate between genotypic and phenotypic resistance (Almecija, 2022). In the case of amitraze, two mutations related to the observation of a loss of efficacy were described by the Spanish team (Hernandez-Rodriguez, 2022). More recently, Rinkevich et al. (2023) have shown a good relationship between the mutation observed in the United States and resistance to this molecule. Research is underway on varroa populations in France to link certain mutations o the octopamine and tyramine receptors. Genetic testing is currently based on individual analysis of varroa mites, which takes time and results in significant cost. In order to overcome these constraints, the LNR is also working on the possibilities of analysing pools of varroa mites from the same colony/apiary. The advantage of genetic methods of resistance detection is that dead varroa mites can be used. ITSAP and ADA AURA are also involved in a project to study the resistance of Varroa to acaricides (SEMIVAR project). **The FNOSAD** mentions practical difficulties in implementing phenotypic resistance tests: 1) there must be enough **live** varroa mites, which is not always easy to obtain, and often possible only towards the end of July – August, 2) i.e dates when the laboratory's working capacities are limited or exceeded, and when it is often no longer possible to order the appropriate VMPs (*via* the PSEs in particular) 3) the cost of these analyses is high (€200-300) and must be covered by the FNOSAD's own funds. => A test on dead varroa mites for both amitraze and tau-fluvalinate would be easier to implement. **The article published by the FNOSAD in Bee Health from May-June 2023** ("Varroa control drugs: results of 2022 efficacy tests, and developments since 2007" LSA no. 315) **assesses at only 37% cases where the efficacy of amitraze reaches the 95% threshold, compared to 67% in 2021 (test on 129 colonies).**		Could RFSA stimulate at national level the development of research and testing in case of resistance issues? ➢ Research on galenic forms better suited to molecule diffusion kinetics (repeated rather than prolonged exposure to varroa mites present in the brood). Release of actives not always "repeatable" in strips. **ANMV Info:** Expectations of flash effectiveness of strips are often disappointed, but this is normal as it takes 6 to 10 weeks to see the effect. (see APIVAR or APITRAZ SPC in section Route of administration and dosage: "In the presence of brood, strips must only be removed after 10 weeks of treatment.") ➢ Details on diffusion of the actives in the hive could be further investigated.	

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	A working group (WG) from the Epidemiosurveillance in Animal Health platform is interested in the surveillance of Varroa (and the viruses transmitted by this parasite). A focus on monitoring Varroa's resistance to acaricides was proposed in the WG objectives. **ANMV info:** the number of PhV declarations is relatively limited and ± stable (around 30/year) since 2017. An increase to 50 cases is noticed in 2019 in connection with the establishment of the network of the Observatoire des Mortalités et des Affaiblisements de l'Abeille mellifère (OMAA). In 2022, 58 reports of lack of efficacy were received for varroa treatments, including some fairly well-documented reports from veterinarians. However, overall, the information did not allow us in 2/3 of the cases to conclude that the drug was ineffective (generally due to a lack of objective infestation data). Furthermore, the performance and results of any sensitivity tests were generally not mentioned in the reported cases. In the absence of data on colony infestation levels, other causes of treatment failure such as excessive parasitic pressure at the time of treatment could not be excluded. The ANMV points out that no "flash" effect of the strips is claimed and that it is necessary to wait 6 to 10 weeks before obtaining a sufficient reduction of the parasitic population. (see APIVAR or APITRAZ SPC § Route of administration and dosage: "When brood is present, strips should only be removed after 10 weeks of treatment.") Since the last meeting, several documents were produced and published: a guide document on the ANSES website, an article in "La Santé de l'abeille" to promote pharmacovigilance and an article in the GTV Bulletin on Good Practices for the use of VMPs against Varroa. The document with the important elements to be declared has been online on the ANMV website since 2022. For the FNOSAD declarations, we have seen with Florentine Giraud to have more exhaustive data about the apiaries concerned for the cases declared since 2022. In 2023, only 27 cases of lack of efficacy were reported (all drugs combined), 13 of which concerned efficacy tests carried out by the FNOSAD in 2021. Warnings regarding the risk of resistance are mentioned in the SPC of VMPs, containing tau-fluvalinate or amitraze.			

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	It should be noted that the problems encountered in France have not necessarily been reported in other European countries.			
	• **"Illegal" use of pure oxalic acid** (much cheaper). Artisanal manufacture of glycerin-based strips. The fact that some beekeepers use this type of treatment all year round could lead to a risk of developing resistance over time.		3 AMM for the use of oxalic acid in dripping (with the new VARROXAL MA dated 08/09/23). Use also possible in sublimation for APIBIOXAL and VARROXAL and in spraying for VARROXAL.	
Virosis	- DWV (Deformed Wing Virus) plays an important role in Varroa-related morbidity (associated with Varroa control). The therapeutic challenges are linked to the fight against Varroa. - Chronic Bee Paralysis due to CBPV (Chronic Bee Paralysis Virus) is also a disease with high prevalence. Many viruses identified but not always with clinical consequences. No treatment for these virosis.	0 VMP	Research on interfering RNA (MRL honey). The limits are currently the difficulties of application and the cost of this type of treatment.	**m**
American Foulbrood	No drug allowed. But risks of illegal use of antibiotics, leading to the development of resistance and problems of contamination of honey (residues).	0 VMP	No need for chemical drugs (tetracyclines prohibited (no MRL), and inactive on spores of *Paenibacillus larvae*). Satisfactory treatment by transfer, change of strains, rules of sanitary measures. Research project based on the vaccination of queens. Could be interesting see the Salmela & Freitak publication, 2018 (Nordic patent filing) https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1005015. **ANMV note:** A conditional authorization was granted in the US and Canada for a vaccine marketed in 2023: Our Product – Dalan Animal Health. See article 2022: Frontiers | The oral vaccination with *Paenibacillus larvae* bacterin can decrease susceptibility to American Foulbrood infection in honey bees—A safety and efficacy study (frontiersin.org), and article in Bee Health No. 314 (Colin, 2023). The requirements for vaccines are different in Europe and the US, particularly in terms of efficacy levels. Foulbrood management methods are also different in Europe and the US. **LNR:** Presentation of the product at various meetings organised with : Anses – Sophia Antipolis (which is the reference laboratory for France & UE and for WOAH),WOAH, DGAL and FNOSAD. Efficacy which was assessed under laboratory conditions (larval rearing), is assumed to be average (30-50%). Effectiveness field data are still	**m**

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			needed. Research is underway to develop vaccines for other diseases (European foulbrood and brood mycosis) **FNOSAD note post 2021 meeting:** Interest of bacteriophages (see figures below)? T. S. Brady *et al.*, 2017. Bacteriophages as an alternative to conventional antibiotic use for the prevention or treatment of *Paenibacillus larvae* in honeybee hives. *Journal of Invertebrate Pathology*, Volume 150, Pages 94-100, ISSN 0022-2011. SB Santos *et al.*, 2019. Identification of the first endolysin cell binding domain (CBD) targeting *Paenibacillus larvae*. *SCI Rep.* 2019 Feb 22;9(1):2568. doi: 10.1038/s41598-019-39097-2. Note that bacteriophages are expressly named in Appendix II of the New Regulation 2019/6 as Innovative Therapies. Given the uncertainties associated with the change in management of this disease (implementation of LSA, discontinuation of sanitory measures), it may one day be useful to have a drug control available provided that it is easy to use (easier than a transfer for example) and not too expensive (and with all the qualities of a drug).	
European foulbrood	No drug allowed. Cases becoming more frequent, more recurrent, or more virulent (see ECLEA study conducted by the LNR: 2017-2019). The OMAA has identified some persistent cases in Brittany and Pays de Loire.	0 VMP	Same as American foulbrood.	**m**
Nosemosis	Nosemosis at *N. apis* (symptomatic) seems to have disappeared in favour of *N. ceranae* (less symptomatic, weakening factor in the context of co-exposures). Rarely diagnosed. **LNR:** A case has been highlighted in the North-East of France in 2023, with remission. Zootechnical measures difficult only on large bee population or reduced manpower. No VMLPs. No MRL for fumagillin (but not really necessary).	0 VMP	Numerous biotechnical methods can be used to manage the emergency (change of queen, displacement and ventilation of the hive). There is no real need for medication as it would be difficult to prescribe a treatment to fight a disease that is very difficult to diagnose, as Nosema is considered by many to be opportunistic. Algae polysaccharides in prevention? Interest? efficiency? https://www.sciencedirect.com/science/article/abs/pii/S0144861715006517	**m**
Acarapisosis due to *Acarapis woodi*	This disease is rarely diagnosed in France (disappeared due to treatment against Varroa?). 2 cases recently reported: one in Isère (diagnosed in 2022 and 2023) and one in Pays de la Loire (2023). Concerning the case in Isère, the symptoms are marked and increasing in the apiaries concerned. The case in Pays de la Loire was rather a chance discovery with other diseases clinically predominant in the apiary (CBPV in particular).	0 VMp	Treatment with off-label volatile anti-varroa VMPs *via* the "cascade" (e.g. thymol-based VMPs, FORMICPRO and APIBIOXAL or VARROXAL in sublimation)	

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Therapeutic gap: resolution in progress **with existing solution**	**Initial problem**	**Type of problem**	**Solution / Alternatives** **Reason for:** **Resolution in progress / Disappearance of the therapeutic gap**	**GAP initially** **Major: M** **minor: m**
Varroosis (caramelization for APIBIOXAL by sublimation)	• **Problem with APIBIOXAL by sublimation** (by professional beekeepers) => caramelization ++ every 5 administrations. Working time & risks ++ for the user (explosion for Sublimox type devices). Efficacy that depends on the device: Varrox-eddy device from a Swiss laboratory for oxalic acid powder, but low efficacy (<50%) with APIBIOXAL (according to FNOSAD test). Other Italian devices (Oxalika Premium* or Oxalika Pro-Easy**) refer to use with APIBIOXAL. **ANMV Info:** We recorded 5 identical cases in 2021 (several sources but similar narrative that mentioned a possible obstruction of Sublimox-type devices), but which did not fall under PhV *stricto sensu* because no reported lack of efficacy or adverse effects related to caramelization with APIBIOXAL. It remains to be seen whether a specific mention is needed for APIBIOXAL specifying the risk associated with its use with closed-chamber sublimators such as Sublimox would be necessary. **Interest of Swiss VARROXAL with this device** **=> wish for a French MA** forwarded by the FNOSAD to the marketing holder (Andermatt-Biovet). Their project is a to submit an application in certain countries and then a mutual recognition application (RM) in France.		VARROXAL 0.71g/g obtained a **MA in France (RM) on 08/09/23** There are 3 oxalic acid MAs (with the new VARROXAL MA dated 08/09/23) to be used in dripping, but this administration requires opening the hives, which requires more time and favorable weather. VARROXAL (which contains no sugar) should overcome the caramelization problems observed with APIBIOXAL in sublimation. VARROXAL is not yet widely used due to its recent MA. It can be used in sublimation and spraying. **FNOSAD:** For information, its price was set by Andermatt France just below that of APIBIOXAL (although it was the beekeeping sector that paid for the MRL dossier), i.e. €48 per bottle whereas it is €35 (and €25-27 in wholesale prices) in Switzerland. Improvements of the SPC wording are suggested by the FNOSAD and will be included in the medicinal product technical data sheet. **ANMV Info:** France was not the reference country for the mutual recognition registration procedure for this new VMP. Its SPC must be suitable for the different countries where the drug has been registered. The Southern Europe or Northern Europe references have been used to avoid mentioning specific countries because the climatic conditions may be quite different within the same country.	**M #1**
Varroosis (availability and presentation issues for VARROMED)	• **Significant and undeclared VARROMED shortages**, especially in 2021. Other difficulties with VARROMED: numerous administrations (=> a lot of oxalic acid administered) & poorly designed bottle for correct and accurate administration (unsuitable nozzle which encourages approximation and overdosing, graduation scale not clearly visible). Need to connect to another device or to transfer contents.	Disp	VARROMED has a very significant success with beekeepers because it is the only one that can be used in summer, in organic farming, in the presence or not of brood, and without temperature constraints. There is no reported safety concerns. **ANMV Info:** **No shortages declarations** since the last meeting. The comments concerning the bottle must be reported to the MA holder.	**M #1**
Destruction of hives	Use of sulphur wick or vaporisation of SO_2 (or oil in Anglo-Saxon countries in particular). See publications Mutinelli 2020 (journal OIE) and Roy 2022 (Can Vet J 2022;63:541–544). **ANSES info:** regulatory biocide status of SO_2 not defended to date	(0 VMp)	The objective being **the destruction of hives, this concern moves away from the scope of this hearing on therapeutic gaps.**	

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Prioritisation of gaps by representatives of the veterinary profession (excluding ANMV)

Prioritisation of participants (excluding ANMV) Gaps identified	Samuel BOUCHER	Lionel GRISOT	Florentine GIRAUD	Stéphanie FRANCO	PRIORITIES in 2021 Major: M minor: m
Varroosis	M #1	M #1	M #1	M #1	M N° 1 *
Virosis	m	m +	m	m	m
American Foulbrood	m	m	m	m	m
European Foulbrood	m	m	m	m	m
Nosemosis	m	m	m	m	m
Acarapidosis to *Acarapis woodi*	m	m	m	m	

* (caramelization for APIBIOXAL in sublimation and galenic problems for VARROMED)

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Changes in gaps since the last meeting in October 2021:

Favorable trend for:

- Varroosis:
  - APIBIOXAL caramelization in sublimation: major gap resolved thanks to the granting of MA for a new VMP with pure oxalic acid
  - availability and presentation issues for VARROMED: major gap solved with sufficient supplies

No major change for other major or minor gaps

	Hearing of 15/10/21	Hearing of 18/12/23
MAJOR priorities	1. **Varroosis** **- Reduced efficacy and questioning of certain treatments** - caramelization of APIBIOXAL in sublimation - problems of availability and presentation for VARROMED	1. **Varroosis** **- Reduced efficacy and questioning of certain treatments** **- "Illegal" use of pure oxalic acid** (much cheaper)
Minor Priorities	• American Foulbrood • European Foulbrood • Nosemosis • Virosis	• Virosis • American Foulbrood • European Foulbrood • Nosemosis ✚ ***Acarapis woodi* mites**
Existing solution	➢ Destruction of hives (out of the hearing scope i.e therapeutic gaps)	Varroosis: ☑ APIBIOXAL caramelization in sublimation - **MA (dated 09/23) granted for a new VMP** ☑ problems of availability and presentation for VARROMED **– no more shortages**