

## Therapeutic gaps in the Cattle sector

### Meeting of 27/04/21

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#### The priority gaps identified are:

1. A need for topical treatments: antibiotics for ophthalmic use, teat injuries, etc.
2. Respiratory mycoplasmosis
3. Oral antipyretics for use in dairy farming in particular.
4. Oral tranquilizers.
5. Anti-parasitics adapted to avoid the use via the cascade.

Gaps 1 and 3 mentioned above are essential in terms of animal welfare (AW).

**Phytotherapy:** the sector uses these herbal products a lot for various therapeutic applications. This poses a real problem linked to the absence of MRLs, products without MA, sold as nutritional without adequate control. Food manufacturers offer this type of product through direct sales of dietary products to farmers.

Full of "gurus" who offer a lot of dietary supplements, supervision is necessary even if it is socially very fashionable.

Pathology	Problem* encountered *Economic: E / Cascade: C / Other: O	Type of problem * (E/C/O)	Alternatives identified	NO therapeutic solution identified	PRIORITIES Major: M minor: m
Ocular infections with corneal lesions	<p><b>Big deficiency of VMP approved for such claim. Off-label use of ointments and eye drops</b> intended for other species (e.g. Ophthocycline) or intramammary ointments with fixed WP (withdrawal period of 28days for meat &amp; offals, 7days for milk).</p> <p>DRAXXIN has a marketing authorisation for keratoconjunctivitis but it is prohibited in dairy cows (no MRL defined for milk).</p> <p><b>No ophthalmic ointment with marketing authorisation for cattle, while certain specifications prohibit "off-label" use: <u>therapeutic impasse.</u></b></p> <p>Major problem in the veal calf sector.</p> <p>Debate on the sensitivity of <i>Moraxella</i> to antibiotics and the bacteria responsible for KC</p>	C	Use of intramammary or ophthalmic ointments (with MA for other species). OPHTOCYCLINE or FRADEXAM, accepted by the DGAL with fixed WP. Ophthalmic ORBENIN available in Switzerland but import not possible due to other national alternatives via cascade.		<b>MAJOR 1 (AW)</b>

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<b>Teat injuries (wounds, cracking, scratches, etc.)</b>	<b>The only topical treatment with MA is COTHIVET.</b> DERMAFLON does not treat anything (detergent properties). COTHIVET dries up a lot. Need for healing ointment treatment containing antibiotics.	C	Current use of the combination of COTHIVET/iodine and honey or isolation of the teat. <ul style="list-style-type: none"> <li>• VEGEBIOL (hygiene product but claims like therapeutics &amp; milk smell problem)</li> <li>• SULMIDOL (Sulfapiridine): accepted by DGAL with fixed WP because LMR exists for all species</li> <li>• ZnO Coophavet ointment WP=0 day</li> </ul>		<b>MAJOR 1 bis (AW)</b>
<b>Respiratory mycoplasmosis</b>	<b>Absence of vaccine in France.</b> Still no mycoplasma vaccine. Problem +++ Real concern about the treatment and extension of respiratory mycoplasmosis. This pathology was mainly confined to fattening and trading workshops and is now beginning to be found in livestock farming with <b>major resistance problems.</b>	O	UK granted temporary an import authorisation for a US vaccine (self-vaccine?) No import request registered by ANMV. Problem more marked in "fattening". The option of auto-vaccines in veal calves may be too long in the process.	<b>X</b>	<b>MAJOR NO. 2</b>
<b>Oral antipyretics</b>	<b>No MA for oral antipyretics and paracetamol in cattle,</b> only paracetamol MA for pigs (no MRL for bovine). Risk of ulcers in calves with aspirin. Need for oral antipyretics.	C	<b>Possible use</b> (status of "no LMR required" in pigs) <b>with fixed WP (validated by DGAL as LMR status valid for all foodstuffs)</b>		<b>MAJOR 3 (AW)</b>
<b>Oral tranquilizers</b>	<b>Need for oral medication for cattle.</b> Shotgun injection is no longer possible because the appropriate formulation of xylazine (ROMPUN) no longer exists. What's more, shotgun injection is like a circus game! with the responsibility of the person who shoots... A list of essential substances including acepromazine with 6 months of WP (as for equidae) is not feasible (ANMV). <b>No LMR status for acepromazine</b>	C	<b>The use of oral VMP (acepromazine) with MA for horses is illegal (validated by DGAL) and leads to the need for slaughtering/destruction of treated bovine.</b>	<b>X</b>	<b>MAJOR 4</b>
<b>Paramphistomosis</b>	<b>No MA for this indication for cattle:</b> the necessary dose of oxyclozanide is different from that authorised for the treatment of fasciolosis. <b>Wish for a paramphistomosis MA with specific studies</b> on this parasite. Many protocols are proposed without proof of efficacy meeting the MA requirements. No studies available on the efficacy of oxyclozanide on the immature form, the only which is pathogen. The increase in doses causes diarrhoea, hence the current recommendation for a stop-dose (3.5 g per animal).	C	<b>Oxyclozanide used via the cascade.</b> Oxyclozanide belongs to Table 1 with a milk MRL (10 µg/kg) => <b>its use is possible (validated by DGAL) with fixed WP.</b>  Farmers no longer deworm and prefer the use of herbal products (how effective? consumer safety?)		<b>MAJOR 5</b>
<b>Dicrocoeliosis</b>	<b>No MA for cattle - Albendazole</b> Use via the cascade but with the fixed WP issue. Treatment performed at times when WP is not critical.	C	Use of HAPADEX via the cascade (milk WP is 3 days for cattle) but the dicrocoeliosis MA claim is granted only for sheep.		<b>MAJOR 5 bis</b>

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			<b>Need for an approved claim in cattle, with confirmation of the dose and determination of an appropriate WP.</b>		
<b>Cryptosporidiosis</b>	<p><b>Lack of curative treatment with an approved cryptosporidiosis indication. Off-label use of paromomycin</b> (GABBROVET, PAROFOR). Discomfort zone. Halofuginone has no curative indication (MA for “prevention or reduction of diarrhoea due to <i>C parvum</i> infection”) and needs to be administered on a full stomach, hence the problem in the beef cattle sector. Cost problem in veal calf breeding (=&gt; use of kaolin)</p> <p>In beef cattle sector: very complicated to apply effective measures. Inadequate treatment modalities for suckling calves: 1 time per day for 7 days from the 1st or 2nd day of life; to be administered after the meal. Risk of zoonosis in immunocompromised individuals. The MA in France of 2 VMPs with paromomycin (PAROFOR and GABBROVET) made it possible to get out from the previous situation with the illegal import of belgian GABBROVET but there is still <b>no consensus on the use of this molecule in the absence of an MA. The literature presents several different protocols.</b></p> <p>The situation would become critical in case of AMR (incl. risk in turkey) or in case of availability issues.</p>	C / E / O	<p>Halofuginone (5 VMPs with MA in Fr for prevention or reduction of diarrhoea due to <i>C parvum</i> infection)</p> <p>Kaolin, charcoal in beef calves (cheaper).</p> <p>Field use of “borderline” products.</p> <p>Health and biosecurity</p>	<b>X</b>	
<b>Besnoitiosis</b>	<p><b>No MA for cattle - high-dosed sulphonamides</b> (significantly higher than those currently authorised for cattle =&gt; current presentations unsuitable). Geographical extension, goes up the Rhône valley, linked to commercial transactions (healthy carrier animals). The national territory is almost entirely contaminated. But with low prevalence in general. <b>The urgency is to clean up as quickly as possible. But active research into drug and vaccine development would put us in a more comfortable position.</b></p> <p>Spain is a Eu contaminated country. Lack of efficacy of sulphonamides. Culling of animals and elimination of seropositive animals. <b>Eradication plan in place (SNGTV parasitology commission).</b></p>	O	<p>The outbreaks management policy varies with the regions and national harmonization is not really on the agenda, <b>many departments are beginning to adopt a “living with” approach.</b></p> <p><b>No vaccine available in Europe – 1 vaccine exists in Israel.</b></p>	<b>X</b>	
<b>Piroplasmosis</b>	<p><b>A single VMP with MA = CARBESIA and with a too long meat WP</b> (i.e 213 days, milk WP=6 days). <b>Non-respected WP not respected due to farmers' forgetfulness</b> (meat WP = "crime shoot" for animals in the fattening phase (cull cows in the pasture).</p> <p>For application of treatment, clinical signs are required =&gt; <b>almost no more used as a preventive measure</b> (and yet preventive measures would be necessary when naive animals are introduced into risk areas): too</p>	O / E	<p>Treatments for ticks lower incidence but do not eradicate (for animals that are not immune) and deltamethrin is toxic to aquatic organisms and bees. <b>Individual treatment, preventive use in general for animals of 6 months or on introduced animals.</b></p> <p><b>Different doses for curative/preventive.</b></p>		

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	expensive, with limited efficacy and risk of excessive use of the only drug available. <b>Essential in curative and only available molecule</b> (recurrent shortages until May 2020 – stable since).				
<b>Culicoids: pre-export insect control</b>	<b>Deltamethrin: effectiveness questionable, and real application by farmers even more doubtful...</b>	O	Would it be possible to encourage the <b>development of isoxazoline (a "Bravecto" for calves)</b> ? would also be of interest for biting flies (see below), provided there is no environmental safety issue.		
<b>Flies (stomoxes and others)</b>	<b>Deltamethrin: but development of resistance. The only molecules that can be used, especially in milk production, are pyrethroids, which have been used for several decades.</b> Environmental and resistance issues. No alternative for now. High risk linked to vector borne diseases.	O			
<b>Topical NSAIDs for bruising, trauma, sprains</b>		O	In absence of topical products, hygiene products are sold. No topical capsaicin available (as QUTENZA skin patch in humans).		
<b>Paralyzing gastroenteritis/stomach paralysis</b>	No treatment	O	Erythromycin has gastrokinetic properties.... (but it's an antibiotic...)	X	
<b>Abomasal ulcer</b>	<b>No medicinal products with MA for cattle</b>	C	<b>Omeprazole, existing MRL status for all foodstuffs via oral route</b> ("no MRL required" status for horses). No LMR status requested or established for Cattle but use via the <b>cascade is possible with fixed WP (validated by DGAL).</b>		
<b>Fungal mammals (Candida, Aspergillus, etc.)</b>	No medication Very rare	O		X	
<b>Mastitis caused by algae (Prototheca...)</b>	No treatment Very rare	O		X	

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Resolution in progress	EXISTING solution				
<b>Nodular theilitis</b>			Attempt with injectable iodine without success. Low occurrence, culling when it occurs	<b>X</b>	
<b>Respiratory vaccines against Salmonella</b>	SALMOPAST frequent shortages (not officially since the end of 2018). The 50mL presentation is not very suitable. On these types of vaccines, quality control problems lead to regular shortages. SALMOPAST is also a vaccine against <i>Salmonella typhimurium</i> and <i>S. dublin</i> , it is the only vaccine against <i>Salmonella</i> that claims prevention against clinical forms but does not prevent excretion. <i>Montevideo</i> is not uncommon in cattle and there is no vaccine for this strain.		Auto-vaccine for <i>S. montevideo</i>		
<b>Joint infections</b>	Off-label use of florfenicol: a MA extension for florfenicol is desired. Use with normal dosage. The main issue is a pharmacokinetics one with difficult access of antibiotics at the site of the infection requiring high doses for a long time – which economically prohibits the treatment of adults (and strongly limits that of young animals).		Other authorised antibiotics (in Fr): - lincomycin + spectinomycin (3 VMPs for calves) - oxytetracycline (1 VMP for cattle septic arthritis caused by <i>T. pyogenes</i> , <i>E coli</i> and <i>S. aureus</i> ) - enrofloxacin (5 VMPs for acute arthritis to <i>M. bovis</i> in cattle <2 years and 4 VMPs for arthritis in calves), <b>with uses restrictions of critical antibiotic</b>		
<b>Infections of the peritoneum, kidney, urinary tract and central nervous system.</b>	Antibiotics allowed for other indications. AMPHOPRIM, the only MA for urinary infections with short WP. (Concerns for indications other than respiratory or for bacteria not mentioned in the MA=> off-label use. Issue due to too precise indications)		Infrequent infections (except peritonitis). All new approved antibiotic VMPs only have respiratory infections claim. Problem with dose adjustment. Dairy sector: cascade use not very problematic except in case of WP issue		
<b>Papillomatosis</b>	No treatment. Few problems in the beef cattle sector, more in the dairy sector.		Auto-vaccines could be the solution. Viral "auto-vaccines" are possible for ruminants (via "ATU" with quality data) => communicate more on this option (experienced in poultry on rheovirus). Magnesium widely used with more or less success.	<b>X</b>	
<b>Moth</b>	1 vaccine exists RINGVAC BOVIS, marketing stopped. Remaining shortage, several ATUs delivered to compensate for this. No more MA for treatment (griseofulvine). IMAVERAL: MA for cattle but important labour need. IMAVERAL used locally, acts on lesions already present (leather depreciation). Leather manufacturers pay vaccines directly to slaughterhouses. IMAVERAL is a heavy treatment, difficult to apply. Risk of environmental contamination. Zoonosis.		3 vaccines under ATU (thanks to ANMV reactivity:-), 2 in marketing– need for MA and securing the availability (quota per applicant). Many phyto products are used without proven effectiveness Oral massive iodine intake, knowing that the injectable potassium iodide has a WP=0 day. Which efficiency ????		

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<b>Antispasmodic</b>	SPASMIPUR short WP: 2 days for meat; 12 h for milk. CALMAGINE, DIPYRARGINE, ESTOCELAN and SPASMIZOLE: meat WP=18 days, prohibited in milk. SYMPAGESIC: meat WP=18 days IV, 28 days IM, prohibited in milk		SPASMIPUR (scopolamine) CALMAGINE, DIPYRARGINE (metamizole) ESTOCELAN, SPASMIZOLE, SYMPAGESIC (scopolamine + metamizole)		
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