

Therapeutic gaps in the Cattle sector

Hearing of 30/05/23

Participants: Olivier Fortineau (dairy cow vet practitioner, SNGTV veterinary medicinal products (VMPs) commission), Corinne Jaureguy (beef calf vet practitioner, SNGTV drugs commission), Jacqueline Bastien (vet practitioner in Auvergne, SNGTV drugs commission, member of the CSMV) and Lionel Grisot (vet practitioner in Franche Comté, member of the CSMV).

for ANMV: L. Baduel, B. Leroux, H. Ait Lbacha, M. Salery, J. Bietrix, L. Fabry. **Excused:** S. Barreteau, C Guittré

Reminder of the responsibility for the comments made during the hearing and reported in this report:

- The identification of therapeutic gaps (and the details of the situations expressed and the alternatives envisaged) are 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 "ANMV info: ..." to distinguish the origin of the words expressed.

The priority areas identified by the representatives of the veterinary profession present are:

1. **A need for topical antibiotic treatments: for local administration in case of ocular infections, teat injuries, etc.**
2. **Parasiticides for cattle with marketing authorisation (MA), particularly for the paramphistomosis and dicrocoeliosis indications, with appropriate and validated doses and withdrawal times**
3. **Antipyretics and tranquilizers that can be administered *per os*, analgesics that can be used in dairy farming.**

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

New elements since the last meeting – indicated in blue below.

Phyto-Aromatherapy: the sector uses a lot herbal products for various therapeutic applications. This poses a real problem linked to the absence of MRLs, products without MA, food products without controls. Food manufacturers offer this type of product through direct sales of dietary products to farmers. Lots of "gurus" who offer many dietary supplements: supervision is necessary even if it is very fashionable.

ANMV response: Work by the European Commission is planned for 2024 on MRL files for these substances.

Therapeutic gaps in the Cattle sector

Hearing of 30/05/23

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

Pathology	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 <u>appropriate</u> veterinary medicinal products (VMPs) 0 TS: Lack of therapeutic solution	Problem Type: PhV, Disp, Reg 0 VMP 0 TS	Alternatives identified	PRIORITY Major: M minor: m
Ocular infections with corneal lesions	<p>Big deficiency of VMP approved for such claim. Off-label use of ointments and eye drops intended for other non-food producing species (e.g. Ophthocycline) with fixed WP ($\geq 28j$ meat, $\geq 7j$ milk) or intra-mammary ointments.</p> <p>DRAXXIN has a marketing authorisation (MA) for keratoconjunctivitis but cannot be used in lactating cows (<i>restricted use mentioned in tulathromycin MRL status: "Do not use in animals producing milk for human consumption"</i>).</p> <p>No ophthalmic ointment with MA for cattle, whereas certain breeding specifications prohibit "off-label" use of VMPs leading to <u>therapeutic impasse</u>.</p> <p>Major problem in the calf sector Debate on <i>Moraxella</i>'s susceptibility to antibiotics and on the bacteria responsible for KC</p>	0 VMP	<p>Use of intramammarys or ophthalmic ointments (with MA for other species) such as OPHTOCYCLINE (tetracycline) or FRADEXAM (framycetin, dexamethasone), with fixed WP.</p> <p>Ophthalmic ORBENIN available in Switzerland but import not possible due to other national alternatives <i>via</i> the cascade. ANMV Info: The import vets' request is possible for Opticlox ointment which has a MA in NL or Latvia for cattle and KCI (with <i>Moraxella</i> indication in the dutch SPC) - see DGAL FAQ p3 line 1.</p> <p>Vets, however, are reluctant to submit requests "due to the administrative burden and difficulty of contacting a Latvian or Dutch distributor. A request to extend MA in France would be the best solution".</p>	MAJOR N°1 (AW)
Deep and superinfected teat trauma (wounds, cracking, scratches, etc.)	<p>The only topical treatment with MA is COTHIVET.</p> <p>DERMAFLON does not treat anything (detergent properties). COTHIVET dries up a lot. Need for healing ointment treatment containing antibiotics.</p>	1 VMP	<p>Current use of the combination of COTHIVET/iodine and honey or isolation of the teat.</p> <ul style="list-style-type: none"> VETEBIOL (hygiene product but claims like therapeutics & milk smell problem) SULMIDOL (Sulfapiridine): accepted by DGAL with fixed WP because MRL exists for all species <p><i>*Benefit of using VETRAMIL, but insufficient if an antibiotic is needed.</i></p>	MAJOR N°1 bis (AW)
Paramphistomosis	<p>No MA for this indication for cattle: the necessary dose of oxyclozanide is different from that authorised for the treatment of fasciolosis.</p> <p>Wish for a paramphistomosis MA with specific studies 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.</p>	0 VMP	<p>Oxyclozanide used <i>via</i> the cascade. Oxyclozanide belongs to Table 1 with no restrictions on use in dairy females</p> <p>ANMV Info: "Cascade" use possible at dry-off with 2 doses 3 days apart, with a fixed milk WP ≥ 7 days (i.e 1.5 x 4.5 days) for RUMENIL and ≥ 11 days for other VMPs also indicated for sheep with a milk WP of 7 days.</p>	MAJOR N°2

Therapeutic gaps in the Cattle sector

Hearing of 30/05/23

	<p>The increase in doses causes diarrhoea, hence the current recommendation for a stop-dose (3.5 g per animal). Practitioners wonder whether the current fixed WP according to Reg 2019/6, lower than the previously prescribed WP of 28 days, are sufficiently safe (commitment of the prescriber's responsibility). The MA for this indication or at least depletion studies with published recommended dose would be useful.</p>		<p>The FLUKIVER SPC only mentions the indication <i>Paramphistomum spp.</i> for sheep (with meat WP of 107 and 77 days in cattle) and mentions (§ 4.11 Withdrawal period) "Do not administer to dairy cattle producing milk for human consumption, including during the drying period. " Farmers no longer deworm and prefer the use of herbal products (how effective? consumer safety?)</p>	
Dicrocoeliosis	<p>No MA for cattle - Albendazole MA for cattle and sheep, but dicrocoeliosis indication only for sheep. Application of the cascade with usual WP if the dosage used is the MA's one. As a reminder: Cascade use of HAPADEX (milk WP of 3 days for cattle) is no longer possible as it has not been on the market for several years (in France).</p>	<p>0 VMP Disp</p>	<p>Need for a cattle MA, with confirmation of the dose and determination of an appropriate WP</p>	<p>MAJOR N°2b</p>
Oral antipyretics	<p>No MA for oral antipyretics in cattle. Paracetamol MA only for pig (no MRL required with restriction of oral use _no MRL for cattle). Some integrators prohibit off-label use of VMPs in their specifications. Risk of ulcers in calves with aspirin => mixed with bicarbonate in the field. ANMV Info: There is a MA for an oral ketoprofen for cattle: DINALGEN 300 MG/ML ORAL SOLUTION FOR CATTLE AND PIGS with a meat WP of 1 day (risk of ulcers mentioned in §4.5 of the SPC).</p>	<p>(0) VMP</p>	<p>Possible cascade use of paracetamol with restriction of oral use. ANMV Info: The WP to be applied depends on the WP of the VMP used. It must therefore be clearly defined: there are WP of 0 and 1 day, which will lead to a respective fixed WP of at least 1 or 2 days. Cascade use of oral meloxicam is possible (MA for horses with WP of 3 days and MA for pigs with WP of 5 days).</p>	<p>MAJOR N°3 (AW)</p>
Oral tranquilizers	<p>Need for oral VMPs for cattle. 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... No LMR status for acepromazine. The use of oral VMPs (acepromazine) for horses is illegal and results in the slaughter/destruction of treated cattle. The cascade use of DOMOSEDAN GEL 7.6 MG/ML for horses does not meet the need, as the administration is individual and sublingual.</p>	<p>0 VMP</p>	<p>Potential interest of an oral administration of azaperone? Currently only available for the injectable route</p>	<p>MAJOR N°4</p>
Long-term analgesics	<p>Wish for long-term analgesics to meet animal welfare (AW) considerations, especially for groups of heifers, animals going to summer pastures...</p>		<p>Potential interest of Butorphanol? Butorphanol tartrate listed in Table 1 "no MRL required" for equidae, only intravenously.</p>	
Besnoitiosis	<p>No MA for cattle - high-dosed sulphonamides (significantly higher than those currently authorised for cattle => current presentations unsuitable). Geographical extension, goes up north of France, linked to commercial transactions (healthy carrier animals). The national territory is almost entirely contaminated. But with low prevalence in general.</p>	<p>0 VMP</p>	<p>The outbreaks management policy varies with the regions and national harmonization is not really on the agenda, many departments are beginning to adopt a "living with" approach. No vaccine available in Europe – 1 vaccine exists in Israel.</p>	<p>minor</p>

Therapeutic gaps in the Cattle sector

Hearing of 30/05/23

	<p>The urgency is to clean up as quickly as possible. But active research for drug and vaccine development would put us in a more comfortable position. Spain is a Eu contaminated country. Lack of efficacy of sulphonamides. Culling of animals and elimination of seropositive animals. Eradication plan in place (SNGTV parasitology commission).</p>		<p>Extension of clusters throughout France. In the absence of satisfactory vaccines and/or treatments, the current approach is health-related with the attempt to eradicate "super spreaders" (see ppt Ph. Jacquet at JNGTV 2023).</p>	
Piroplasmosis	<p>A single VMP with MA = CARBESIA and with a too long meat WP (i.e 213 days, milk WP=6 days). WP not respected due to farmers' forgetfulness (meat WP = "crime shoot" for animals in the fattening phase (cull cows in the pasture). For application of treatment, clinical signs are required => almost no more used as a preventive measure (and yet preventive measures would be necessary when naive animals are introduced into risk areas): too expensive, with limited efficacy and risk of excessive use of the only drug available. Essential in curative and only available molecule (recurrent shortages until May 2020 – stable since). ANMV Info: No new shortages reported since last product return in 07/2021.</p>	1 VMP Reg	<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. Individual treatment, preventive use in general for animals of 6 months or on introduced animals. Different doses for curative/preventive. Illusory in practice.</p>	minor
Culicoids: pre-export desinsectisation	<p>Deltamethrin (off-label indication): efficacy perceived as random on the field, and real application by farmers even more doubtful...</p>	0 VMP	<p>Would it be possible to develop an isoxazoline (a "Bravecto" for calves) ? It would also be of interest for biting flies (see below), provided there is no environmental safety issue. There would be a marketing authorisation for cattle in the USA. ANMV Info: The environmental toxicity of isoxazolines and their persistence is proven (cf literature; moreover, this family of substances meets the EFSA criteria for classification as PFAS).</p>	minor
Flies (stomoxes and others)	<p>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. Safety issues for the user, for the environment and resistance risks. No alternative for the time being. High risk associated with vector borne diseases Problems especially for calf horn flies and also for biting or chewing lice. ANMV Info: Since 2021, only one reported case of lack of efficacy on flies and 8 cases of lack of efficacy with deltamethrin-based drugs for other indications (mainly lice). Keep in mind that these are old products, with known and multifactorial efficacy issues (parasitic pressure in the environment in particular), and not often declared by vets.</p>	PhV	<p>Avoid fibrous foods that are excellent substrates for flies. Improvement of buildings. Use of biocides against flies. Biological control with wasps. Pay attention to the under-dosing of treatments linked to an under-evaluation of the weight of animals and the risk of licking with the pour-on/spot-on.</p>	

Therapeutic gaps in the Cattle sector

Hearing of 30/05/23

Topical NSAIDs for bruising, trauma, sprains	No topical medication => animal welfare (AW) issue	0 VMP	In absence of topical products, hygiene products are sold. No topical capsaicin available (as QUTENZA skin patch in humans). ANMV Info: MA dated 17/08/20 for the homeopathic medicinal product TRAUMEEL gel. Ruminants are not mentioned in target species (which are dog, cat, horse): cascade use possible with fixed WP of 1 day (as meat and milk WP of 0 days in horse).	minor
Fungal mammals (Candida, Aspergillus, etc.)	No medication Very rare	0 VMP		minor
Mastitis caused by algae (<i>Prototheca</i>)	No treatment Very rare	0 VMP		

Therapeutic gaps in the Cattle sector

Hearing of 30/05/23

Therapeutic gap: resolution in progress with existing solution	Initial problem of the sector	Type of problem	Solution / Alternatives Reason for: Resolution in progress / Disappearance of the therapeutic gap	GAP initially Major: M minor: m
Respiratory mycoplasmosis	<p>Absence of vaccine in France. Still no mycoplasma vaccine. Problem +++</p> <p>Real concern about the treatment and extension of respiratory mycoplasmosis. This disease was mainly confined to fattening and trading farms and we are starting to find some in breeding with major resistance problems.</p> <p>UK granted temporary import authorisation for a US vaccine (auto-vaccine?)</p> <p>No import request registered by ANMV.</p> <p>Problem more marked in "fattening" farms.</p> <p>The option of autovaccines in beef veal may be too long in the process.</p>	0 VMP	<p>Following the need reported in the last meeting in 2021, ATU requested and granted from 07/2021 then MA delivered to PROTIVITY on 03/05/23:</p> <p>MA granted but vaccine not yet marketed => previous ATU has just been renewed: the vaccine remains available.</p> <p>Live attenuated vaccine for active immunisation of calves from 1 week of age to reduce clinical signs and pulmonary damage caused by <i>Mycoplasma bovis</i> infection.</p> <p>The vaccine protocol includes two SC injections of 2 mL with a 3-week interval.</p> <p>Very good results in bullocks fattening. For beef calves, the cost is high.</p> <p>Since it is a live attenuated vaccine, avoid any previous treatment.</p>	MAJOR N° 2
Cryptosporidiosis	<p>Lack of curative treatment with a cryptosporidiosis indication. Off-label misuse of paromomycin (GABBROVET, PAROFOR). Discomfort zone.</p> <p>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.</p> <p>Cost problem in beef calves farming (=> use of kaolin)</p> <p>Beef cattle sector: very complicated to apply effective measures.</p> <p>Inadequate treatment modalities for "under-the-mother" calves: 1 time per day for 7 days from the 1st or 2nd day of life; to be administered after the meal.</p> <p>Risk of zoonosis in immunocompromised individuals.</p> <p>The marketing of 2 specialities with paromomycin (PAROFOR and GABBROVET) has made it possible to move away from the previous situation with the illegal import of Belgian GABBROVET but there is still no consensus on the use of this molecule in the absence of a MA. The literature presents several different protocols.</p> <p>Critical if antibiotic resistance (+ risk in turkey) or in case of availability issues.</p>	Reg	<p>Gap resolved with MA of 20/06/22 for GABBROVET multi 140 mg/mL solution for pre-ruminant cattle and pigs with colibacillose indication (Dosage: 25-50 mg/kg/day for 3 to 5 days. Meat and offal WP: 20 days) and cryptosporidiosis (dosage: 150 mg/kg/day for 5 days. Meat and offal WP: 110 days).</p> <p>For use in kids, a fixed WP of 165 days is a problem.</p> <p>Crypto dosage not always used in the field (see info JNGTV 2023) – A communication would be beneficial to recall the origin and justification of this dosage.</p> <p>Halofuginone (5 VMPs with MA <u>to prevent or reduce diarrhoea due to <i>C parvum</i> infection</u>)</p> <p>Kaolin, charcoal in beef calves (less expensive)</p> <p>Field use of "borderline" products.</p> <p>Hygiene and biosecurity</p>	minor

Therapeutic gaps in the Cattle sector

Hearing of 30/05/23

Gastroenteritis / abomasum paralysis	No treatment Erythromycin has gastrokinetic properties.... (but it's an ATB...)	0 VMP	Gap resolved by MA of 29/03/21 NEOSKILAB SOLUTION FOR INJECTION FOR CATTLE, SHEEP, GOATS AND HORSES (neostigmine) for ruminal and intestinal atony in cattle, sheep and goats.	minor
Abomasum ulcer	No WMPs with MA for cattle Omeprazole, MRL status for oral administration (no MRL required for horses).	0 VMP	No omeprazole MRL status established for cattle but cascade possible with fixed WP (validated by DGAL) . WP meat ≥ 2 days for oral paste and 3 days for EQUIZOL gastroresistant granules. But cost ++ and SPC § 4.11 "Milk: do not use in milk-producing animals intended for human consumption." Omeprazole listed in Table 1 for horses with no MRL required and restricted to oral use.	minor
Ringworm	1 vaccine exists RINGVAC BOVIS, marketing stopped. Still on shortage, several ATUs issued to compensate for this. More MA for treatment (griseofulvine), Imaveral: MA for cattle but strong workload needed. IMAVERAL used locally, acts on lesions already present (depreciation of the leather). Leather manufacturers pay vaccines directly to slaughterhouses. IMAVERAL is a treatment difficult to apply. Risk of environmental contamination. Zoonosis. 3 vaccines under ATU (reactivity:-), 2 marketed – need for MA and supply security (quota per laboratory). Many phyto products are used without proven effectiveness. Oral use of massive iodine. Knowing that potassium iodine in injectable has a WP=0. Efficiency????	Disp	TRICHOLOR (AMM 18/05/22) , new Ceva vaccine against bovine moth BOVIGEN T (AMM 04/2021) from Virbac, placed on the market after disposal of units under the ATU. Return on the market for BOVILIS Ringvac but suspension due to Brexit.	
Respiratory vaccines against Salmonella	Frequent shortages of SALMOPAST (not officially since the end of 2018). 50 mL 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 salmonella that claims prevention against clinical forms but does not prevent excretion. <i>S. montevideo</i> is not uncommon in cattle and there is no vaccine for this strain.	Disp	NB: Ongoing shortage of SALMOPAST since the end of February 2023, return at the end of August 2023 in principle, communication of critical termination on the ANMV site. Autovaccine for <i>S. montevideo</i> (no requests to date).	

Therapeutic gaps in the Cattle sector

Hearing of 30/05/23

Changes in gaps since the last meeting in April 2021:

Favorable trend for:

- Respiratory mycoplasmosis, major gap resolved thanks to the granting of ATU then of MA for a live attenuated vaccine
- Cryptosporidiosis, thanks to the recent granting of a MA for the treatment in pre-ruminant cattle
- Gastroenteritis /abomasum paralysis, thanks to the recent granting of an MA for intestinal and ruminal atony
- Ringworm, thanks to the recent granting of MA for 2 new vaccines

No major change for other major or minor gaps

	Meeting of 27/04/21	Meeting of 30/05/23
MAJOR priorities	1. Ocular infections with corneal lesions 1. bis Teat trauma 2. Respiratory mycoplasmosis 3. Oral antipyretics 4. Oral tranquilizers 5. Paramphistomosis 5. bis Dicroceliosis	1. Ocular infections with corneal lesions 1. bis Teat trauma 2. Paramphistomosis 2. bis Dicroceliosis 3. Oral antipyretics 4. Oral tranquilizers + long-term analgesics
Minor Priorities	<ul style="list-style-type: none"> • Cryptosporidiosis • Besnoitiosis • Piroplasmosis • Culicoids: pre-export desinsectisation • Flies • Topical NSAIDs for bruising, trauma, sprains • Gastroenteritis / abomasum paralysis • Abomasum ulcer • Mastitis of fungal origin or caused by algae 	<ul style="list-style-type: none"> • Besnoitiosis • Piroplasmosis • Culicoids: pre-export desinsectisation • Flies • Topical NSAIDs for bruising, trauma, sprains • Abomasum ulcer • Mastitis of fungal origin or caused by algae
Resolution in progress	➤ Nodular thelitis (thanks to new vaccine – MA 2019)	➤ Respiratory vaccines against Salmonella (rupture in follow-up)
Existing solution	➤ Respiratory vaccines against Salmonella ➤ Joint infections ➤ Peritoneal, kidney, urinary tract, CNS infections ➤ Papillomatosis ➤ Ringworm ➤ Antispasmodic	<input checked="" type="checkbox"/> Respiratory mycoplasmosis, thanks to ATU then MA (03/05/23) new vaccine <input checked="" type="checkbox"/> Cryptosporidiosis, thanks to the new MA dated 20/06/22 for treatment <input checked="" type="checkbox"/> Gastroenteritis /abomasum paralysis, thanks to the new MA (29/03/21) <input checked="" type="checkbox"/> Ringworm, thanks to 2 new vaccines

Therapeutic gaps in the Cattle sector

Hearing of 30/05/23